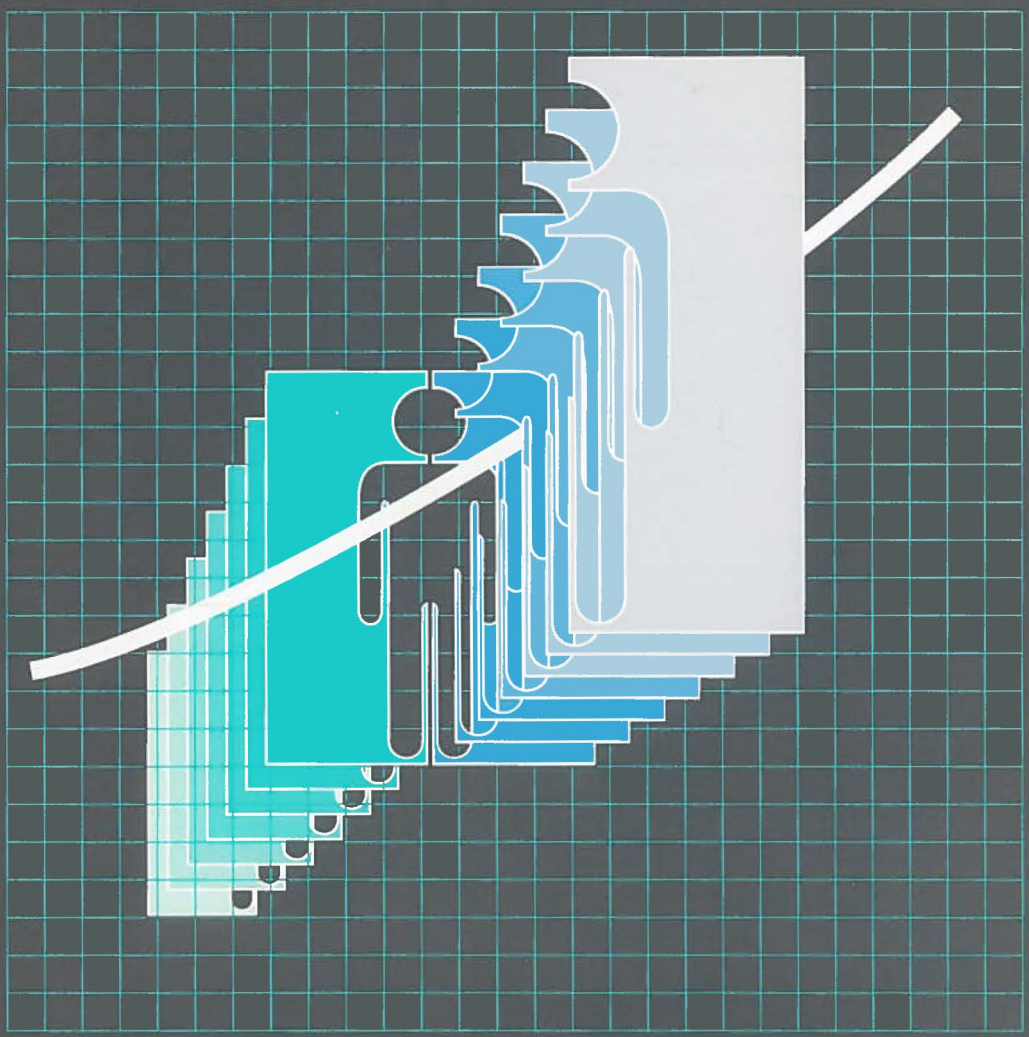
GROWTH OF CHILDREN WITH CANCER



R.Y.J. TAMMINGA

STELLINGEN

1. De incidentie van groeihormoon deficiëntie na schedelbestraling wordt niet alleen bepaald door stralendosis, fractionering en leeftijd van de patiënt, maar ook door de methode en het tijdstip van testen.

2. Ondanks de beschikbaarheid van pneumococcenvaccinatie, verdient een partiële splenectomie bij de stagering van M.Hodgkin, nog steeds overweging.

3. Reconstructie d.m.v. een endoprothese na locale verwijdering van een maligne beentumor, is niet vergelijkbaar met die d.m.v. een rotatieplastiek, daar de eerste een beensparende behandeling betreft en de tweede een vorm van amputatie is.

4. Medische polemologie behoort een vaste plaats te krijgen in de opleiding tot arts.

5. Longmetastasen onzichtbaar op een conventionele röntgen foto maar ontdekt d.m.v. een CT-scan, kunnen bij Wilms' tumor patiënten leiden tot overbehandeling.

6. De kliniek is vaak anders dan de statistiek.

7. Bij de beslissing om een kind met het syndroom van Down voor acute lymfatische leukemie te behandelen, dient het feit dat deze kinderen na het bereiken van een complete remissie dezelfde overlevingskansen hebben als kinderen zonder het syndroom van Down, te worden meegewogen.

8. Zolang Sesamstraat moet wijken voor voetbal, wordt kindertelevisie niet als volwassen beschouwd.

9. De invloed van de biologische klok op effectiviteit en toxiciteit van chemotherapie, verdient meer aandacht.

10. Toediening van adriamycine zodanig dat minder hoge piekspiegels worden bereikt dan na bolusinjectie, mag dan aangetoond minder cardiotoxisch zijn, het behoud van effectiviteit is nog onvoldoende vastgesteld.

11. Onderzoek naar de oorzaak van een mogelijk maligne halslymfeklier d.m.v. een lymfeklierpunctie, kan een lymfeklierbiopsie niet vervangen en kan daarom alleen maar vertragend werken.

12. Een groot nadeel van de screening op congenitale hypothyreoïdie in Nederland, is het hoge percentage dat een tweede hielprik moet ondergaan en dat wordt verwezen naar de kinderarts zonder dat er sprake is van hypothyreoïdie.

13. Een arts die 50% werkt, moet wel voor 100% bijblijven.

14. Behandeling nadat "informed consent" is verkregen, is een kwestie van ethiek, niet van mondigheid van de patiënt.

15. Mensen genezen van jeugdkanker moeten als normale leden van de maatschappij worden geaccepteerd.

GROWTH OF CHILDREN WITH CANCER

Stratification

group	diagnosis	treatment included	median age	(range)
followed from diagnosis (project A):				
1	brain tumor	cranial irradiation >30 Gy spinal irradiation >30 Gy (6/9)*	9.5	3.5-14.7
2	ALL high risk**	cranial irradiation 18 or 24 Gy consolidation (cyclophosphamide/ara-c) prednisone 2 weeks alternated with MTX/6-MP 5 weeks, for 2 yrs	4.5	2.4-10.4
3	ALL standard risk	cranial irradiation 18 or 24 Gy prednisone 2 weeks alternated with MTX/6-MP 5 weeks, for 2 yrs	5.3	1.6-14.0
4	ALL standard risk	3 methotrexate courses (2 g/m^2) dexamethasone 2 weeks alternated with MTX/6-MP 5 weeks, for 2 yrs	5.6	2.4-12.2
5	Wilms' tumor	abdominal irradiation 10-20 Gy (6/9)* actinomycin D/vincristine for $^1/_2$ - $1^1/_2$ yrs	3.4	1.2- 8.3
6	osteosarcoma B-cell NHL T-cell NHL rhabdomyosarcoma Ewing's sarcoma histiocytosis X	high dose methotrexate (>6 g/m^2) and/or cyclophosphamide (>0.3 g/m^2) treatment period: 1-2 yrs	9.6	2.8-15.7
followed from completion of therapy (project B):				
7	ALL standard risk	cranial irradiation 24 Gy prednisone 2 weeks alternated with MTX/6-MP 5 weeks, for 2 yrs	8.3	4.8-13.4
8	osteosarcoma Ewing's sarcoma rhabdomyosarcoma histiocytosis X liposarcoma	high dose methotrexate (>6 g/m^2) and/or cyclophosphamide (>0.3 g/m^2) treatment period: 1-2 yrs	9.8	4.1-12.8

ALL acute lymphoblastic leukaemia.
NHL non Hodgkin's lymphoma.
* 6 out of 9 patients.
** leucocytes in peripheral blood >50,000/mm^3 and/or mediastinal enlargement and/or CNS involvement

RIJKSUNIVERSITEIT GRONINGEN

GROWTH OF CHILDREN WITH CANCER

Proefschrift

ter verkrijging van het doctoraat in de Geneeskunde
aan de Rijksuniversiteit Groningen
op gezag van de Rector Magnificus Dr. L.J. Engels
in het openbaar te verdedigen op woensdag 21 maart 1990
des namiddags te 4.00 uur.

door

RIENK YDE JOHAN TAMMINGA
geboren op 29 november 1953 te Meppel

Promotores:	Prof. G.B. Humphrey, M.D., Ph.D.
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Aan Trijntje, Nienke en Menno

"A child's growth rate reflects, better than any other single index, his state of health and nutrition ....."

P.B. Eveleth and J.M. Tanner[1]

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CHAPTER 1

INTRODUCTION

1.1 RATIONALE

The overall 5 year survival for children with cancer has considerably increased during the past decades and is nowadays about 50%.[2] This result has been achieved by using a combination of surgery, radiotherapy and most importantly chemotherapy. The increase in the long term survival rate and cure rate have caused the focus of attention to be shifted more and more to those patients that survive. Since growth and development are keystone elements in a child's life, quality of life studies should always include these elements. Growth retardation during treatment and catch-up growth after completion of therapy have been reported.[3-10] However, the identification of treatment regimes that have a major adverse impact on growth is not at all complete, especially because longitudinal prospective studies are rare. The ultimate result of these studies might provide reasons for abandoning toxic regimes where regimes with equal or even better cure rates exist.

1.2 OUTLINE OF THE STUDY

In 1980 the divisions of endocrinology and oncology of the Department of Pediatrics, and the statistics group of the Department of Mathematics (University of Groningen) started a study to investigate the growth of children with cancer both prospectively and longitudinally.

In a period of 4 years (1982-1986) all children with a newly diagnosed cancer and histiocytosis X between the ages of 1 and 16 could enter our study. In addition, patients completing treatment for these diseases could participate; however, only during the first 2 years. Thus, it was possible to investigate growth during treatment (project A) and after completion (project B). Patients of non-caucasian origin and those who had disorders influencing growth or sexual development, were excluded.

The data which were collected are given in table 1.1. We studied the same anthropometric variables as used in a study conducted by W.J. Gerver.[11] The anthropometric measurements were collected according to the guidelines of Cameron[12] (see appendix), every three months, after informed consent had

Table 1.1 Data collected

Anthropomorphic variables:	Characteristics of pubertal development:
height and weight	girls and boys: - appearance of axillary hair
armspan	- pubic hair stage
sitting height	
	girls: - onset of menses
circumference of - head	- breast stage
- calf	
- upper-leg	boys: - testicular volume
- upper-arm	
	Hormone levels:
length of - upper-arm	testosterone
- fore-arm	oestradiol
- hand	DHEAS
- tibia	LH/FSH
- foot	
	X-ray of the left hand
biacromial diameter	
biiliacal diameter	

been obtained from patient and/or parents. The measurements were performed by two observers who were replaced twice during the study. The measurements were carried out at hospital admission or when the patient came for a regular visit to the outpatient department. We tried to eliminate systematic daily variations in the measurement results by measuring the patients at the same time of the day.[13] This was, however, not feasible in all cases.

We also took some measurements of the parents of the participating patients, which enabled us to account for genetic influences on e.g. height.[14]

The measurements obtained from children approaching or during puberty may give rise to problems of interpretation. It was for this reason, and because cancer treatment is known to impair the sexual functions in adults,[15] that the development of secondary sex characteristics was also recorded at each visit.

In addition, X-rays of the left hand were made with intervals of 1 year, on the hypothesis that growth impairment might occur concomitantly with impairment of bone age development.

Blood specimens for the estimation of hormone levels were collected only at routine venapunctures. Blood samples obtained randomly during the day for estimation of growth hormone levels are not conclusive and were therefore not measured. The measurement of somatomedin levels was not part of the study, because at the time of outlining the study, the assay was not available to us.

Adverse effects of cancer treatment are among others nausea, vomiting, loss of appetite and an increased susceptibility to infections. Malnutrition and intercurrent infections may contribute to growth retardation. Therefore the occurrence of serious infections, hospital admissions and nutritional support requirements were recorded.

The follow-up period was set to 2 years, because the treatment period could last up to 2 years. There was the option to take measurements beyond that period up to 5 years after the initial diagnosis, with intervals of 1 year however. All collection of data was stopped at April 1988, 2 years after the last patient entered the study. A survey of the data collected from all patients observed from the initial diagnosis onwards is given in figure 1.1. A similar survey was made for patients who were observed from the completion of treatment onwards, although with them the collection of data started at variable times after diagnosis, depending on the duration of treatment.

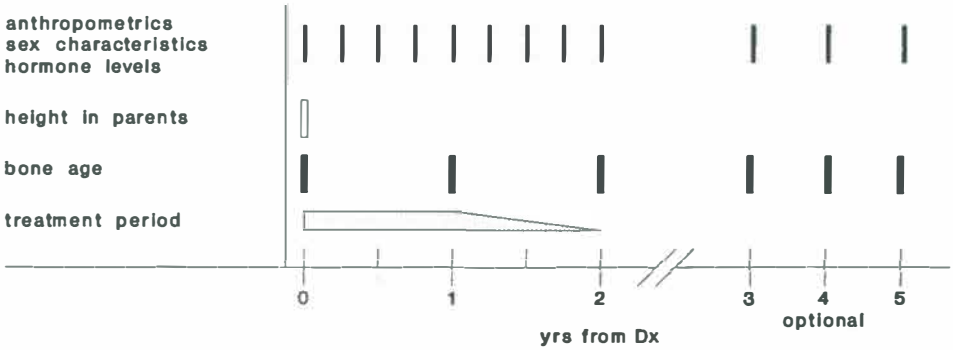


Figure 1.1 Data collection scheme for patients followed from diagnosis; the period of treatment varied in general between 1 and 2 years (for details see table 1.3).

1.3 CONTROL GROUPS

It is often important to include a control group in a study like this. The measurement results of patients can then be compared with those of the control group. Therefore it was considered to take measurements from a sibling or a schoolmate of the patients. This idea was rejected, however, mainly for practical reasons, but also because the differences between the various groups of patients seemed more interesting than the differences between a group of patients and a group of healthy children. Moreover, we expected that children who had only received surgical treatment could serve as controls for the other patients. Unfortunately, the number of patients treated with only this modality appeared to be too small.

A comparison of our patients with healthy children was, however, still possible, because we could compare our results with those recorded in the study of W.J. Gerver.[11,16] This contemporary reference study concerned healthy children from the town of Oosterwolde, like our hospital located in the northern part of The Netherlands. Because this study is cross-sectional, additional information

concerning the longitudinal aspects of growth was necessary if growth curves of patients were to be studied. This information could be obtained from a mixed-longitudinal study, which was performed in the town of Nijmegen, which is located in the south of The Netherlands.[17,18]

1.4 PATIENTS, STRATIFICATION AND NUMBER OF REALIZED MEASUREMENTS

A total number of 130 children was enrolled in the study between March 1982 and April 1986; 104 entered at diagnosis (project A) and 26 at the completion of the therapy (project B). These numbers are rather low because not all eligible patients could be included due to the fact that only a limited number of appointments could be made (for reasons of logistics and manpower). Another restricting factor was that no patients could enter project B after completion of project A.

Originally a stratification in six strata (groups) was proposed for both projects (table 1.2). This stratification was based on a presumed growth-retardation risk during treatment. The hypothesis that was to be validated and that was based on work of other researchers,[3,10] was that during therapy most growth retardation occurs in group I while no growth retardation would occur in group VI.

Table 1.2 Originally planned stratification

group	treatment included
I	cranial irradiation >25 Gy
II	cranial irradiation <25 Gy
III	high dose methotrexate
IV	high dose cyclophosphamide
V	other chemotherapy
VI	no chemotherapy

The small number of patients in some groups made it necessary, however, to revise this stratification. The revised stratification consisted of strata (groups) 1-6 for project A and 7-8 for project B. Similarly, we hypothesised to find most growth retardation in group 1 and gradually less retardation in the subsequent groups 2-6 (table 1.3). A catch-up growth was expected in the groups 7-8.

The revision resulted in the exclusion of 13 patients; among these were the two patients of the original group VI (table 1.2) who were treated with surgery only and who would have served as internal controls; the other 11 patients who were excluded had received therapy that differed from that of other patients. Moreover, a group of 7 patients with acute non-lymphoblastic leukaemia became too small for analysis due to referrals to the bone marrow transplant centre and relapses.

We confined the analysis to those patients who got into and stayed in a first continuous complete remission during the study. The reason for this selection

Table 1.3 Revised stratification

group	diagnosis	treatment included
followed from diagnosis (project A):		
1	brain tumor	cranial irradiation >30 Gy spinal irradiation >30 Gy (6/9)*
2	ALL high risk**	cranial irradiation 18 or 24 Gy consolidation (cyclophosphamide/ara-c) prednisone 2 weeks alternated with MTX/6-MP 5 weeks, for 2 yrs
3	ALL standard risk	cranial irradiation 18 or 24 Gy prednisone 2 weeks alternated with MTX/6-MP 5 weeks, for 2 yrs
4	ALL standard risk	3 methotrexate courses (2 g/m^2) dexamethasone 2 weeks alternated with MTX/6-MP 5 weeks, for 2 yrs
5	Wilms' tumor	abdominal irradiation 10-20 Gy (6/9)* actinomycin D/vincristine for $^1/_2$ - $1^1/_2$ yrs
6	osteosarcoma B-cell NHL T-cell NHL rhabdomyosarcoma Ewing's sarcoma histiocytosis X	high dose methotrexate (>6 g/m^2) and/or cyclophosphamide (>0.3 g/m^2) treatment period: 1-2 yrs
followed from completion of therapy (project B):		
7	ALL standard risk	cranial irradiation 24 Gy prednisone 2 weeks alternated with MTX/6-MP 5 weeks, for 2 yrs
8	osteosarcoma Ewing's sarcoma rhabdomyosarcoma histiocytosis X liposarcoma	high dose methotrexate (>6 g/m^2) and/or cyclophosphamide (>0.3 g/m^2) treatment period: 1-2 yrs

ALL acute lymphoblastic leukaemia
NHL non Hodgkin's lymphoma
* 6 out of 9 patients
** leucocytes in peripheral blood >50,000/mm^3 and/or mediastinal enlargement and/or CNS involvement.

was that growth retardation persisting long after diagnosis, would then be more likely to be due to treatment than to (recurrent) disease. Because of this reason, another 31 patients were not included in the analysis of the longitudinally obtained data (table 1.4).

Table 1.4 Number of patients entered on study, relapsed and evaluated.

group	#of patients entered	relapsed	evaluated
1	14	5	9
2	10	3	7
3	15	2	13
4	15	2	13
5	11	2	9
6	21	9	12
7	13	5	8
8	11	3	8

Table 1.5 Number of patients (male/female) and age at study entry (yrs) per group.

group	M/F	median age	(range)
1	4/5	9.5	3.5-14.7
2	3/4	4.5	2.4-10.4
3	4/9	5.3	1.6-14.0
4	6/7	5.6	2.4-12.2
5	3/6	3.4	1.2- 8.3
6	7/5	9.6	2.8-15.7
7	3/5	8.3	4.8-13.4
8	2/6	9.8	4.1-12.8

Table 1.6 Realized scheduled height measurements.

group	measurements realized (%)
1	91
2	81
3	90
4	80
5	88
6	83
7	90
8	89

Some characteristics of the 79 evaluable patients are presented in table 1.5.

For a proper analysis, the collection of the anthropometric data at equidistant times, without missing data was thought to be needed. Allowing a deviation of 2 weeks, 80-91% of the height measurements were performed according to schedule in the evaluable patients (table 1.6). We considered it practically impossible to increase this percentage. The percentage of realized measurements concerning armspan and sitting height, however, is lower because the equipment was not yet available at the beginning of the study. It is clear that the statistical analysis as originally planned had to be adapted.

1.5 SUMMARY OF THIS THESIS

The main goal of the study was to describe and analyse the growth of children with cancer during and after treatment. The results of the most important anthropometric measurements (height, weight, sitting height, armspan, upper-arm circumference and head circumference) obtained during 2 years of follow up, are presented and discussed in chapter 6. In the preceding chapters we will discuss the precision of taking anthropometric measurements (chapter 2), the methods used for analysis (chapters 3 and 5) and the results of the anthropometric measurements at the time of diagnosis (chapter 4). In the following

chapters we report on our findings concerning the development of bone age (chapter 7) and puberty (chapter 8). The conclusions and perspectives based on the findings reported in the chapters 4 and 6-8 are discussed in chapter 9.

CHAPTER 2

THE PRECISION OF THE ANTHROPOMETRIC MEASUREMENTS

2.1 INTRODUCTION

In general it is pertinent to growth studies and to longitudinal ones in particular, that the quality of the measurements is investigated, especially when more than one observer is involved. The most important aspect of quality control is that information is collected about the reliability of the measurement process as a whole. The results should be used to improve the quality of future observations or to correct, or even ignore, past observations. In the course of our growth study, we performed two separate reliability studies concerning all the anthropometric variables measured.

2.2 OUTLINE OF THE EXPERIMENTS

The first study (1) concerned the reproducibility of measurements by the same observer (intra-observer reliability). This entails the problem of comparing the reproducibilities of one observer with those of another observer.

Twelve healthy schoolchildren participated in study 1; 6 boys and 6 girls, with an age range of 6-12 years. The anthropometric measurements (see table 2.1) were performed at school by two trained observers, according to the guidelines of Cameron[12] (see appendix). All measurements were taken twice, separated by one hour, on each of four consecutive days, for each child. The measurements at a specific day were carried out by the same observer. Such precautions were made that the observers were not aware of previous results. The two observers were employed alternately on the four consecutive days for each child (in the order: 1212 or 2121). The design results in data of the form

$$x_{hijk} \ (k=1,2;\ j=1,2;\ i=1,2;\ h=1,\ldots,12)$$

for each of the separate anthropometric variables. Here x_{hijk} is the k-th measurement by observer j on day i in child h. (Note that some recoding of i is involved: if the order of observers was 2121 then (j,i)=(2,2) corresponds with the second day of observer 2, the third measurement day for the child.)

In the second study (2) we compared measurements of the same individual performed by two different observers (inter-observer reliability).

Nine patients, similar to those in our growth study, participated; 5 boys and 4 girls, with an age range 2-15 years. The same anthropometric variables were measured as in study 1, again by two observers; the measurements were taken at the outpatient department of our hospital. Each patient was measured twice on the same day, once by each of the two observers. These measurements were repeated one week later. This design results in data of the form

$$x_{hij} \ (j=1,2;\ i=1,2;\ h=1,...,9)$$

for each of the separate anthropometric variables. Here x_{hij} is the measurement by observer j on day i in patient h.

2.3 ANALYSIS

With respect to study 1 the model

$$x_{hijk}=\mu_{hij}+e_{hijk}$$

is postulated. Here μ_{hij} is an unknown mean value while e_{hijk} represents the measurement error. Note that the "true" value μ_{hij} is the same for k=1,2 because the two measurements were performed at almost the same time. We postulate that the measurement errors e_{hijk} are independent and identically distributed, e_{hijk} having the distribution $N(0, \sigma_j^2)$. The reproducibility of the measurements is studied by estimating σ_1^2 and σ_2^2. The null hypothesis H: $\sigma_1^2=\sigma_2^2$ that both observers are equally precise, will be tested as well. The estimates will be based on these 24 differences for each observer:

$$x_{hij2}-x_{hij1} \ (=e_{hij2}-e_{hij1}) \text{ with } N(0, 2\sigma_j^2).$$

An unbiased estimator for σ_j^2 is:

$$\hat{\sigma}_j^2=\sum_{h=1}^{12}\sum_{i=1}^{2}(x_{hij2}-x_{hij1})^2/48.$$

Under the null hypothesis H: $\sigma_1^2=\sigma_2^2$ the test statistic

$$F=\hat{\sigma}_2^2/\hat{\sigma}_1^2$$

has Fisher's $F_{24,24}$ distribution. The null hypothesis is rejected (at level .05) if the outcome of F is sufficiently small (F<0.44) or sufficiently large (F>2.27).

With respect to study 2, the model

$$x_{hij}=\mu_{hi}+\nu_j+e_{hij}$$

is postulated. Here μ_{hi} is the "true" value on day i for patient h, ν_j is the bias of observer j, and e_{hij} is the measurement error. We postulate that the e_{hij} are

independent and identically distributed, e_{hij} having the $N(0, \sigma_j^2)$ distribution. Note that it is not possible to test the null hypothesis H: $\nu_1=\nu_2=0$ that both observers are producing unbiased measurements. It is possible, however, to test the null hypothesis H: $\nu_2=\nu_1$ that there are no systematic differences between the two observers. The test is based on these 18 differences:

$$x_{hi2}-x_{hi1} (=\nu_2-\nu_1+e_{hi2}-e_{hi1}) \text{ with } N(\nu_2-\nu_1, \sigma_1^2+\sigma_2^2).$$

The Student one-sample statistic

$$t=\sqrt{n}.\hat{\mu}/\hat{\sigma}$$

can be applied to the n=18 differences obtained. Here $\hat{\mu}$ denotes the mean of these 18 differences and $\hat{\sigma}$ the natural estimate of the standard deviation, $\sigma=\sqrt{(\sigma_1^2+\sigma_2^2)}$. The null hypothesis H: $\nu_1=\nu_2$ is rejected if the outcome of Student's t-test is sufficiently small or sufficiently large when tested in the t-distribution with 17 degrees of freedom ($t_{17;.025}=2.11$).

2.4 RESULTS

The results of the reliability studies are presented in table 2.1. Note that the measuring of weight was not included in these studies and that armspan was only measured in the second study. The estimate $\hat{\sigma}$ of the standard deviation of the differences of the measurement results, has been divided by $\sqrt{2}$ ($\hat{\sigma}_e=\hat{\sigma}/\sqrt{2}$) resulting in an estimate of the standard deviation of the measurement error (also referred to as the "technical error of measurement").

Some additional figures from the literature are included in the table for reference purposes: $\hat{\sigma}_a$ and $\hat{\sigma}_b$ for intra-observer reliability and $\hat{\sigma}_c$ for inter-observer reliability. The estimate $\hat{\sigma}_a$ of the standard deviation of the measurement error of the Oosterwolde reference study[11] is obtained after dividing the standard deviation of the differences published there by $\sqrt{2}$. In that study one observer performed only a part of the measurements; 71 children were measured twice; the second series of measurements was carried out by the same observer within 30 minutes from the first series.

The estimates $\hat{\sigma}_b$ and $\hat{\sigma}_c$, available for only some of our variables, are derived from the Health Examination Survey (HES) in the United States;[19] that study serves as an internationally accepted standard study as mentioned by Cameron.[12] The data for the HES study were gathered in the period of 1963-65 and published in 1973. Replicate measurements were performed in 301 children, with a time lapse of 2-3 weeks; 224 children were measured twice by the same observer and 77 children by two different observers.

Table 2.1 Results of intra- and inter-observer reliability.

growth parameter	study 1			study 2			reference studies		
(mm)	$\hat{\sigma}_1$	$\hat{\sigma}_2$	F	$\hat{\mu}$	$\hat{\sigma}_e$	t	$\hat{\sigma}_a$	$\hat{\sigma}_b$	$\hat{\sigma}_c$
height	4.03	4.42	.98	2.67	4.02	1.99	2.42	4.94	6.81
armspan				8.44	7.59	3.34*	5.54		
sitting height	4.31	7.75	.32*	-.39	3.69	-.32	3.46	5.35	7.05
head circumf.	2.03	2.36	.71	1.78	2.31	2.31*	1.92		
calf circumf.	2.32	1.89	1.02	5.06	1.81	8.40*	3.03		
upper-leg circumf.	6.50	3.82	3.06*	1.61	5.23	.93	4.60		
upper-arm circumf.	1.77	1.89	.89	4.06	5.01	2.43*	2.33	8.72	3.40
upper-arm length	6.69	5.24	1.66	10.39	8.34	3.74*	3.46		
fore-arm length	3.45	4.00	.72	-4.33	9.73	-1.34	2.53	5.44	9.15
hand length	1.96	1.62	1.46	2.44	2.80	2.62*	2.33	1.17	1.54
tibia length	2.32	1.89	.52	1.44	5.26	.82	2.55	1.06	2.44
foot length	2.68	1.95	1.94	2.67	1.68	4.76*	1.48	2.64	5.24
biacromial diameter	2.90	4.32	.43*	-.33	6.40	-.16	2.25	5.44	9.15
biiliacal diameter	4.12	3.08	2.18	.38	3.71	.29	1.15	7.11	15.45

$\hat{\sigma}_1$ ($\hat{\sigma}_2$) estimate of standard deviation of intra-observer measurement error in observer 1 (observer 2).
F statistic for testing that both observers are equally accurate; limits for testing at level .05 are .44 and 2.27.
$\hat{\mu}$ estimate of mean of differences between two different observers.
$\hat{\sigma}_e$ estimate of standard deviation of inter-observer measurement error.
t statistic for testing that there are no systematic differences between both observers; limits for testing at level .05 are ± 2.11.
$\hat{\sigma}_a$ estimate of standard deviation of intra-observer measurement error in the Oosterwolde reference study.[11]
$\hat{\sigma}_b$ estimate of standard deviation of intra-observer measurement error in the Health Examination Survey.[21]
$\hat{\sigma}_c$ estimate of standard deviation of inter-observer measurement error in the Health Examination Survey.[21]
The F and t statistics are marked with an asterisk when the outcome was significant.

2.5 DISCUSSION

The results of study 1 in table 2.1 show that observer 2 is significantly more precise than observer 1 for upper-leg circumference and less precise for sitting height and biacromial diameter. Such differences are not surprising, of course. The estimates $\hat{\sigma}_1$, $\hat{\sigma}_2$, $\hat{\sigma}_a$ and $\hat{\sigma}_b$ of intra-observer standard deviations of measurement errors are quite similar. A few exceptions (with emphasis on a comparison with the HES) deserve attention, however. For example, hand length and tibia length are measured in the HES more precisely than in our study. For some other measurements the precision of our observers is considerably larger than the precision of the HES observers. The anthropometrists involved in our study were instructed to be as precise as possible. They knew that differences between the measurements at different points in time would be decisive in the statistical analyses and that these differences should not be affected by measurement errors.

The main result of study 2 is, that in spite of all precautions and good intentions of the observers, in half of the 14 measurements a statistically significant systematic difference between v_1 and v_2 could be established (see the column with t-values). The relevance of these results has to be discussed in the context of practical application. The systematic error ($\hat{\mu}$) of about 1 cm (10.39 mm, table 2.1) in upper-arm length is considerably larger than the standard deviation of the measurement error derived from repeated measurements by the same observer in study 1 ($\hat{\sigma}_1 \approx \hat{\sigma}_2 \approx 6$ mm). Moreover, it is only slightly smaller than the standard deviation of upper-arm length in the population of healthy children of the age of ten (15 mm[11]). In sum, this shows that the measuring of upper-arm length is unreliable. It appears that the two observers work with different interpretations of the guidelines of Cameron.

The second largest systematic error concerns armspan (8.44 mm, table 2.1); this error is larger than the standard deviation of the measurement error in the Oosterwolde reference study ($\hat{\sigma}_a$=5.54), and about one eighth of the standard deviation of armspan in the population of healthy children of 10 years old (68 mm[11]). Here the statistical and systematic errors are not a problem at all if the aim is to establish whether or not the armspan of a child is atypical for its age. The effect of the measurement errors becomes more problematic if more subtle questions are examined, e.g. with respect to proportional atypicalities or with respect to the growth of a particular child in a relatively short period of time. (A boy of 10 years old increases his armspan each month by about 5 mm on average.[11])

The next largest systematic error (5.06 mm) concerns calf circumference with a t-value of 8.40. The practical relevance of this error lies somewhere between that of upper-arm length and armspan considered earlier. The standard deviation of calf circumference in the population of healthy children of 10 years old (22 mm[11]) is about 4 times as large as the systematic error.

The other statistical significances established (foot length, hand length, upper-arm circumference and head circumference) seem less disturbing. Note, however, that in our longitudinal growth study, the development of such children is studied over a period of just 2 years. Variables like head circumference display almost no growth and are extremely sensitive to shifts of measurement protocol or transitions from one observer to another.

Apart from these main results of study 2, we might also consider the estimates $\hat{\sigma}_e$. These estimates should be compared with the estimates $\hat{\sigma}_c$ of the standard deviation of the inter-observer measurement error of the HES. From a global point of view the results are similar and deserve no further discussion.

To sum up, it may be stated that the results of our intra- and inter-observer reliability study suggest that even dedicated well-trained observers may display differences in precision (study 1) and systematic errors (study 2). However, most of the statistical significances established are not really alarming from a

practical point of view. Moreover, we intend to restrict the analysis in our growth study to only some anthropometric variables such as height, weight, sitting height, armspan, and circumference of upper-arm and head.

CHAPTER 3

STANDARD DEVIATION SCORES

3.1 INTRODUCTION

An obstacle in comparing physical properties of growing children is that they differ with regard to age and sex. The same problem also holds for our patient groups. To deal with this obstacle, the original measurements were replaced by standard deviation scores (z-scores). The computation is as follows:

$$z=(x-\mu)/\sigma$$

Here x indicates a measurement result in a patient, e.g. his height, μ denotes the mean of the measurement in the reference population of healthy individuals of the same age and sex as the patient, and σ denotes the standard deviation of the measurement in this population.

This transformation into z-scores has the effect that the transformed measurements of a sample from the reference population follow the standard normal distribution, i.e. that with a mean 0 and variance 1, at least approximately. This means that if for a particular patient group the mean z-score is found to be significantly above zero, the average measurement result of the patient group is larger than in the comparable reference population; similarly, if the standard deviation of z-score is significantly above 1.0, this indicates that the variability of the measurements in the patient group is larger than in the reference population. Transformation into z-scores will be used in the analysis of the cross-sectional data at diagnosis (chapter 4) and in the analyses of the longitudinal data (chapter 5 and 6).

3.2 THE REFERENCE POPULATION

The choice of the reference population for transformation into z-scores is very important. Some, possibly conflicting, considerations are as follows. (1) The reference population should be as close as possible to the population our patients come from, including time, place and social structure, (2) the measurements studied by us have to be examined for the reference population as well, (3) the measurement techniques should be as similar as possible, (4) the sample size of the reference population should be as large as possible. An-

other consideration is whether the data of the reference population are collected cross-sectionally or longitudinally. It is obvious that a cross-sectional study may be adequate to study measurements at diagnosis, but it is equally obvious that some additional information is needed if longitudinal growth patterns are to be examined.

It was obvious to choose the cross-sectional Oosterwolde study[11] as our reference. This study was performed in 1979-1980 and was based on measurements in 1246 boys and 1105 girls with an age range of 0.0-17.7 years, all children living in the same part of The Netherlands where our hospital is located. All the measurements performed by us were also examined in the Oosterwolde study. We considered the measurements of the children involved in the Oosterwolde study representative for those of our patients, at least if the growth of our patients would not be affected by disease or treatment.

3.3 ANALYSING CROSS-SECTIONAL DATA OF HEALTHY CHILDREN

To investigate the reliability of the transformation into z-scores on the basis of the Oosterwolde reference study, we needed additional data of healthy children. Such data were taken from the Nijmegen mixed-longitudinal growth study.[17] A sample of 34 children was composed by taking one boy and one girl at random out of each age category (4, 4.5, 5,...,12 years). One girl was omitted from the analysis (not, however, from the analysis of weight for height), because her z-scores for most anthropometric variables were below -3.

The results of the analysis of the measurements at study entry i.e. when the first measurements (cross-sectional data) were taken, are presented in table 3.1. Note that armspan was not measured in the Nijmegen growth study.

Table 3.1 Mean z-score (m) and its standard deviation (sd) of various anthropometric variables measured cross-sectionally in a sample of 34 (33) children taken from the Nijmegen growth study. The Oosterwolde study served as reference population. The t-values concern testing whether the mean z-score is significantly different from zero.

variable	n	m	sd	t-value
height	33	-.27	1.03	-1.51
weight	33	-.21	1.00	-1.21
weight for height	34	-.06	.95	-.37
upper-arm circumference	33	-.59	.90	-3.77 *
sitting height	33	-.49	.91	-3.09 *
head circumference	33	-.41	1.06	-2.22 *

* denotes significant finding at level p=0.05.

Table 3.2 Means (m) and standard deviations (sd) of various anthropometric variables in boys and girls at the ages of 4, 9 and 14 yrs in the Oosterwolde and the Nijmegen growth study, such as published.[11,17] Also given is the difference (d) between both means and the resulting z-score with the Oosterwolde study as reference.

		Oosterwolde		Nijmegen			
variable	age (yrs)	m (cm)	sd	m (cm)	sd	d (cm)	z-score
boys							
height (cm)	4	107.0	4.5	105.4	4.1	-1.6	-.36
	9	137.6	6.0	136.9	5.3	-.7	-.12
	14	166.5	7.7	166.5	8.4	.0	.00
weight (kg)	4	17.5	2.1	16.4	2.0	-1.1	-.52
	9	29.8	3.7	29.3	4.1	-.5	-.14
	14	50.5	7.7	49.8	9.2	-.7	-.09
upper-arm circ. (cm)	4	17.6	1.2	16.9	1.1	-.7	-.58
	9	19.5	1.4	18.6	1.6	-.9	-.64
	14	23.5	2.2	22.2	2.5	-1.3	-.59
sitting height (cm)	4	61.6	2.3	60.5	2.2	-1.1	-.48
	9	73.8	3.1	73.2	2.7	-.6	-.19
	14	85.7	3.9	85.1	4.3	-.6	.15
head circ. (cm)	4	51.0	1.4	50.9	1.1	-.1	-.07
	9	53.7	1.5	53.4	1.3	-.3	-.02
	14	55.6	1.6	56.1	1.4	.5	.31
girls							
height (cm)	4	106.5	3.6	106.1	4.8	-.4	-.11
	9	137.7	5.9	135.5	6.2	-2.2	-.37
	14	165.4	6.9	164.5	6.7	-.9	-.13
weight (kg)	4	17.3	2.1	17.1	2.3	-.2	-.10
	9	30.3	5.0	28.7	4.3	-1.6	-.32
	14	52.6	7.9	51.1	8.0	-1.5	-.19
upper-arm circ. (cm)	4	16.7	1.4	16.7	1.4	.0	.00
	9	20.1	1.8	18.8	1.6	-1.3	-.72
	14	24.3	2.3	22.6	2.3	-1.7	-.74
sitting height (cm)	4	61.2	2.2	60.3	2.8	-.9	-.41
	9	73.3	2.9	72.4	2.7	-.9	-.31
	14	86.8	3.4	86.1	3.4	-.7	-.21
head circ. (cm)	4	50.6	1.5	49.3	1.4	-1.3	-.87
	9	53.1	1.5	52.0	1.4	-1.1	-.73
	14	54.8	1.6	55.1	1.6	.3	.19

The t-values given concern the testing of whether the mean z-scores are significantly different from zero. This table displays that the standard deviation of the z-score is always near 1.0, but that the mean z-score of upper-arm circumference, sitting height and head circumference in the Nijmegen children is significantly ($p = .05$; $t_{32;.025} = -2.04$) below zero.

Both this finding and a similar one for the other variables correspond with the general observation that children (and adults) in the northern part of the country are somewhat taller on the average than those in the southern part (table 3.2). This phenomenon might be explained in terms of nature and nurture. A minor role will also be played by differences in measurement technique and by the secular trend. The data collection in Nijmegen started 10 years earlier than in Oosterwolde. Roede and Van Wieringen mention an increase in z-score of height between their cross-sectional nation-wide studies in 1965 and 1980 during the age of 3.0-12.0 years in boys of .18 to .40, and during the age of 3.0-10.0 years in girls from .13 to .40.[20]

The established differences between the Oosterwolde reference study and the Nijmegen growth study illustrate that the choice of a reference population is a delicate one. We have chosen the Oosterwolde study because of the reasons mentioned in §3.2. The cross-sectional character of this study is not a drawback when studying measurements at diagnosis (chapter 4): the corresponding z-scores will be tested in the standard normal distribution to establish differences between patient groups and the healthy population as presented by the Oosterwolde reference study. The methods of analysing growth curves (longitudinal data; chapter 6), will be discussed in chapter 5.

CHAPTER 4

MEASUREMENTS AT DIAGNOSIS

4.1 INTRODUCTION

Several authors have reported on the height of children with cancer at diagnosis. Broomhall et al.[21] were the first to describe that patients with acute lymphoblastic leukaemia (ALL) were taller at diagnosis than their healthy peers. By contrast, Berry et al.[22] reported, that boys diagnosed under the age of 4 years were shorter at diagnosis. However, others have found normal heights.[23-25] Berglund et al.[26] had the opportunity to investigate the height of patients 1 year before diagnosis; at that time, ALL patients were taller than their peers, but at diagnosis their height was normal. The findings in bone cancer patients are as confusing as in ALL patients.[24,27-30] Possible explanations for the differences between the results are the accuracy of the measurements and the nature of the reference population or control group used. In addition the use of significance levels of 5% has been criticised.[24]

Anthropometric measurement results obtained at diagnosis not only provide baseline information for the longitudinal part of our study, but also have an intrinsic value.

4.2 SUBJECTS MEASURED AND DATA OBTAINED

104 children took part in our anthropometric study at diagnosis. Eight patients could not be measured within 14 days of diagnosis. The characteristics of the remaining 96 patients are shown in table 4.1. The patients were categorized for statistical purposes according to table 4.2. Only 68 fathers and 77 mothers could be measured (both parents in 60 cases).

The patients' height, weight, upper-arm circumference, sitting height, armspan and head circumference were measured; of their parents we only measured height. In some cases patient data are incomplete (table 4.3) because of for example unavailability of equipment (sitting height and armspan), logistics, or (rarely) patient factors. A particular reason of a logistical nature for the scarcity of armspan measurements in the leukaemia patients (group A) was that during the first years of the study, these patients were hospitalized in a protected environment during their induction treatment, whereas the armspan measuring

equipment was located somewhere else and could not be transported. Later on patients were allowed to leave their room, e.g. for purposes of investigation.

Table 4.1 Characteristics of 96 children with cancer measured at diagnosis.

diagnosis	number of patients			age (yrs)	
	male	female	total	median	range
ALL high risk	7	4	11	3.3	0.1-10.5
ALL standard risk	15	14	29	4.2	0.9-14.0
ANLL	4	1	5	6.0	2.4-14.1
Wilms' tumor	3	8	11	3.6	1.2- 9.3
osteogenic sarcoma	2	2	4	14.4	14.3-15.7
Ewing's sarcoma	1	2	3	11.4	9.8-13.8
rhabdomyosarcoma	3	1	4	3.3	0.3- 5.5
brain tumor	5	7	12	9.7	3.5-14.7
NHL	7	1	8	5.6	0.1- 9.8
histiocytosis X	2	2	4	2.0	0.8- 9.7
miscellaneous*	3	2	5	3.4	2.3-13.2

* fibrosarcoma, neuroblastoma, malignant histiocytosis, Hodgkin's disease (2).
ALL acute lymphocytic leukaemia; ANLL, acute non lymphocytic leukaemia; NHL, non-Hodgkin's lymphoma.

Table 4.2 Categories and number of patients analysed for measurements at diagnosis.

group	n	diagnosis
A	45	leukaemia
		- ALL
		- ANLL
B	24	solid tumor
		- Wilms' tumor
		- osteogenic sarcoma
		- Ewing's sarcoma
		- rhabdomyosarcoma
		- fibrosarcoma
		- neuroblastoma
C	12	brain tumor
D	15	remaining malignancies
		- NHL
		- histiocytosis X
		- malignant histiocytosis
		- Hodgkin's disease

for abbreviations see table 4.1.

Table 4.3 Number of anthropometric data obtained at diagnosis per group.

measurement	A	B	C	D
height	44	23	12	15
weight	44	24	11	15
weight for height	44	23	11	15
arm circumference	44	22	12	15
armspan	24	12	11	9
sitting height	39	17	11	12
head circumference	44	24	12	14
midparent height	35	12	6	7

4.3 ANALYSIS

We introduced corrections for differences in age and sex between the patient categories by calculating standard-deviation scores (z-scores). For these calculations we used the reference values of the Oosterwolde study[11] (chapter 3).

Furthermore, the midparent height was established (the mean of father's height and mother's height). Again we calculated z-scores, to compare the midparent heights of our patients with the midparent heights in the healthy population. The values of a Dutch, cross-sectional, nation-wide study[20] were used for reference. As a reference mean we used the mean of average normal adult men and average normal adult women ($^1/_2\,\mu_1+^1/_2\,\mu_2$); as the reference standard deviation we used $^1/_2\sqrt{(\sigma_1^2+\sigma_2^2)}$. In a formula it reads as follows:

$$z=x-(^1/_2\,\mu_1+^1/_2\,\mu_2)/^1/_2\sqrt{(\sigma_1^2+\sigma_2^2)}$$

Here x denotes the midparent height of a patient, μ_1 the average height of normal adult men, μ_2 the average height of normal adult women and σ_1 and σ_2 denote the standard deviation of height in normal adult men and women respectively.

To compare the height of the patients with the height of its parents we calculated the difference between the z-score height and the z-score target height by simple subtraction. The target height is defined by Tanner[14] as midparent height plus 6.5 cm for boys or minus 6.5 cm for girls. The z-score target height was calculated by using mean and standard deviation of healthy adult men and women respectively.[20] A positive (negative) result of the subtraction indicates a height larger (shorter) than expected on the basis of the height of the parents. Note, however, that the correlation between height in a child and his midparent height is rather weak.[14]

Statistical analyses of the data were carried out using Student's t-test; a p-level of <0.05 was considered significant.

4.4 RESULTS

Height and weight (or rather weight for height) of each patient are displayed (as z-scores) in the figures 4.1 and 4.2. The patients are categorized according to table 4.1. Note that 2 patients with leukaemia have z-scores for height >3. One patient with a brain tumor (craniopharyngioma) has a z-score for height <-3. Considering weight for height all patients have z-scores within the range of -3 to 3 (figure 4.2). However, especially among the patients with a solid tumor, some had very low weight for height z-scores.

The patients were reclassified for statistical purposes according to table 4.2, because the numbers of patients in some disease categories were rather small. Even then, group C and D remain small, also because of incomplete data

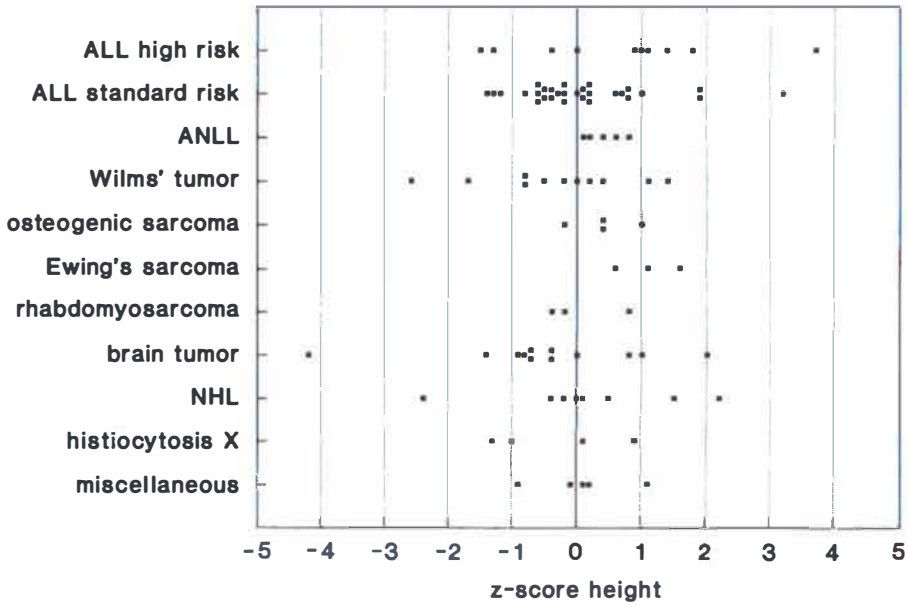


Figure 4.1 Z-score for height in 94 children with cancer at diagnosis; stratification according to table 4.1.

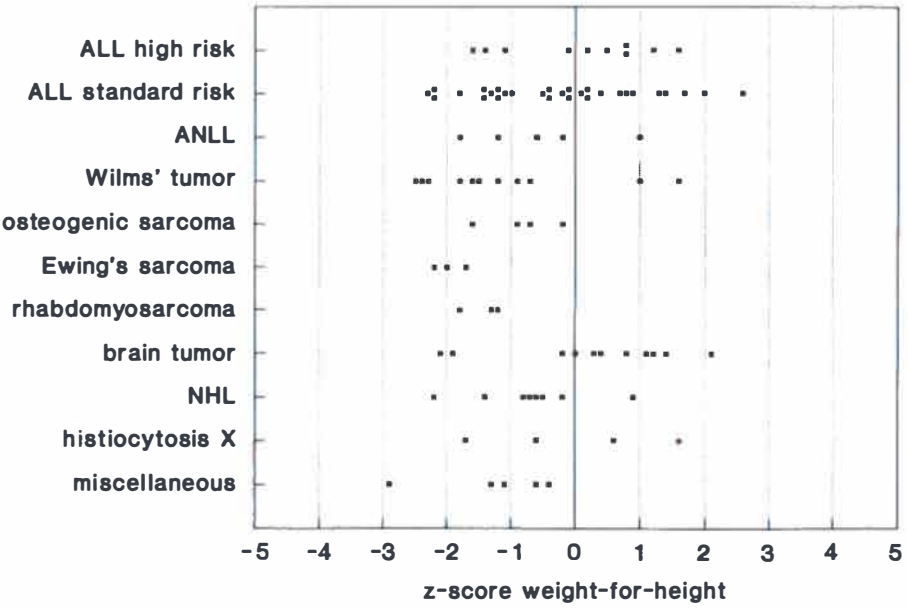


Figure 4.2 Z-score for weight for height in 93 children with cancer at diagnosis; stratification according to table 4.1.

(table 4.3). The means and standard deviations of the z-scores are given in table 4.4. Significant differences with respect to zero (the mean of a standard normal distribution, §3.3) are marked with an asterisk.

Table 4.4 Anthropometric data obtained at diagnosis, presented as z-scores (mean and standard deviation)

measurement	group A		group B		group C		group D	
	mean	sd	mean	sd	mean	sd	mean	sd
height	.25	1.12	.07	.97	-.47	1.53	.03	1.17
weight	.00	1.12	-.55*	.96	-.01	1.40	-.38	1.14
weight for height	-.19	1.22	-1.11*	1.03	.28	1.28	-.67*	1.15
arm circumference	-.71*	1.08	-.70*	.98	.62	1.26	-.80*	1.53
armspan	.83*	1.18	1.18*	1.03	-.33	.98	-.08	.95
sitting height	.22	1.19	.02	.80	-.20	1.26	-.08	1.37
head circumference	.06	.89	-.47*	.91	.00	1.52	-.44*	.63
midparent height	-.16	.90	-.53	1.35	-.21	.68	.00	1.58

* significantly different ($p < .05$) from zero.

The patient groups were compared by means of 2-sample t-tests. Height and sitting height in the groups A and B are not significantly different from the reference population and also not from each other; weight for height is significantly lower in group B in comparison with healthy people but not significantly different from A; arm circumference is in both groups below normal, while armspan is abnormally large in both groups; head circumference is low in group B and significantly different from A. The results in group C show that the arm circumference is normal, though significantly different from that in groups A and B.

The midparent height in all 4 groups is not significantly different from normal. Considering the differences between the z-score for height and the z-score for target height, there are no clear differences between the patient groups (figure 4.3). Only two patients had a z-score of >3 or <-3, which is comparable to the results presented in figure 4.1.

4.5 DISCUSSION

A number of anthropometric measurements in children with cancer was collected at the time of diagnosis. No abnormalities and no differences between the 4 different patient groups were found with respect to height and sitting height. Nor were any noteworthy differences recorded in midparent height and target height.

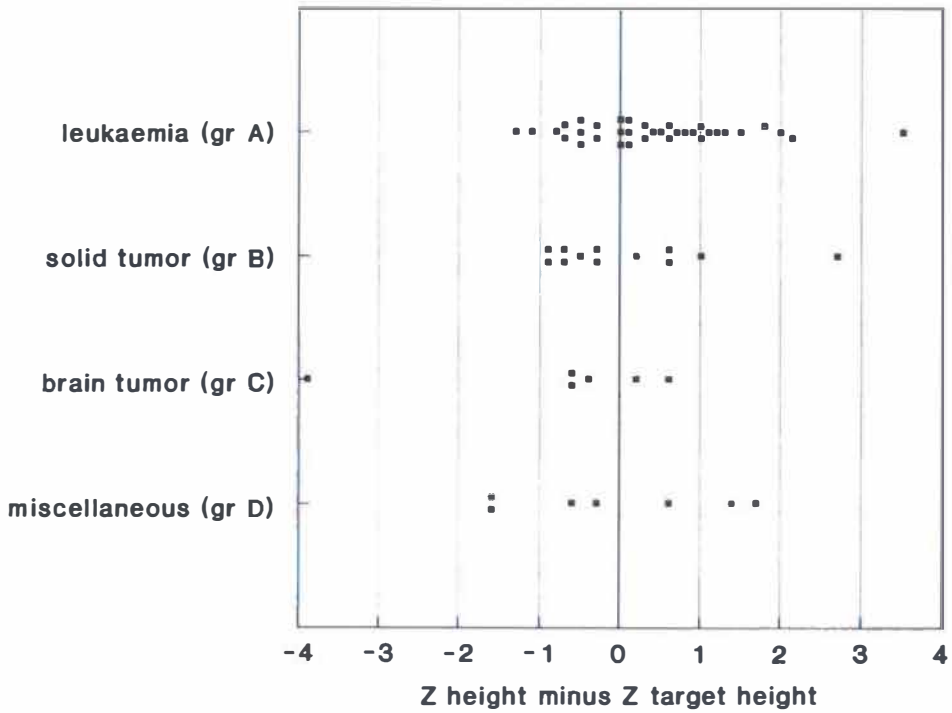


Figure 4.3 Difference between z-score height and z-score target height (midparent height +/- 6.5 cm) in 60 children with cancer; stratification according to table 4.2.

With respect to armspan we found large values in patients with leukaemia and a solid tumor, the values significantly differing from the findings in groups C and D.

In the literature it is suggested that a more than average height and rapid growth are associated with some malignancies (§4.1) and that familial and/or environmental factors may play a pathogenetic role in this.[31] Some reports have mentioned circumstantial evidence for this hypothesis, though cause and consequence cannot always be distinguished. Several investigators have reported on the incidence of cancer in patients treated with growth hormone (GH). There seems to be no increased incidence (of relapses) of brain tumors.[32-34] The incidence of ALL during GH treatment, however, is possibly higher than in the healthy population.[35,36] Some mediators of height growth such as GH and somatomedin, have also been ascribed a pathogenetic role.[37] Although elevated GH levels at diagnosis have been described in leukaemia patients,[22,38] the results concerning somatomedin levels are conflicting.[22,39]

Our results do not support the hypothesis that tallness or rapid growth predisposes to childhood cancer, with the exception of a wide armspan in patients with leukaemia and a solid tumor.

With respect to weight for height, low values were found in solid tumor patients, significantly differing from those in leukaemia patients. This is consistent with previous studies[40] reporting poor nutritional status, and is probably related to the disease itself. Similarly, upper-arm circumference is abnormally low in all patient groups except in that of the brain tumor patients. Arm circumference values parallel the weight for height values only in the patients with a solid tumor. This suggests that arm circumference is an early and sensitive marker for a less optimal nutritional status.

We focussed on measurements at diagnosis, expecting differences among the various diagnostic categories and also between the cancer patients and the healthy children. Though some obvious differences were found (e.g. weight for height) we have come to the conclusion that the number of noteworthy differences was much less than anticipated. What was particularly remarkable was that no relationship was found between increased height and leukaemia, though changes during the last year before diagnosis[26] could not be investigated.

CHAPTER 5

METHODS USED FOR ANALYSING THE LONGITUDINAL DATA

5.1 INTRODUCTION

The main aim of our study was to investigate for various anthropometric measurements whether growth disturbances appear during the 2 years of treatment after the diagnosis (project A) and whether catch-up growth could be registered during the 2 years after the completion of therapy (project B). For this purpose measurements were performed every 3 months during a period of 2 years. The raw scores $x_{i1},...,x_{ip}$ at times (ages) $t_{i1},...,t_{ip}$ of patient i were transformed into z-scores $z_{i1},...,z_{ip}$, using the Oosterwolde study[11] as reference (chapter 3).

The assumption is that a healthy child grows according to a specific growth curve (percentile) and that his z-score, on average, remains the same. Patients, however, may shift from one percentile to another, indicating retardation or catch-up growth. The z-score of such patients will decrease or increase. In the present chapter (§5.3) we will discuss 3 approaches to analyse series of z-scores which were obtained during a period of 2 years: (1) one based on a linear regression, (2) one on a parabolic regression and (3) one on a more complicated function. The theory for these approaches is given as well (§5.2).

In addition, an analysis of the longitudinal anthropometric data of different groups of healthy children from the Nijmegen growth study[17] will be presented (§5.4). This analysis provides information concerning the validity of our approach to transform longitudinal data into z-scores using the cross-sectional Oosterwolde reference study. Moreover, the results of the analysis may be used to compare the growth of different patient groups with the Nijmegen growth study.

5.2 MODELLING

The original plan to analyse our longitudinal data, was based on Rao's model for growth curves.[41] To apply this model to our data it is necessary that the measurements are performed at fixed equidistant points in time. But deviations from the planned measurement schedule could not be avoided (§1.4). Such devia-

tions were e.g. caused by the absence of anthropometrists and by the fact that the appointments for patient care did not always parallel the measurement scheme. Because of these deviations adaptations of the original plan were necessary.

One way out of this problem is to modify the data in such a way that they comply with the theory for the ideal measurement scheme. For example, one might use only 5 instead of 9 equidistant measurement points and calculate the corresponding scores by interpolation or, if necessary, by extrapolation.

It seems more elegant, however, to postulate a growth-curve model for the data (t_{ij}, z_{ij}); $j=1,...,p_i$; $i=1,...,n$, where the measuring points (t_{ij}) are not necessarily 3 months apart and not necessarily nine in number. We make use of the idea that for each patient a linear or quadratic relationship exists, at least approximately, between the z-scores and the times of measurements, for the period of 2 years. Hence either the linear regression

$$z_{ij}=a_i+b_i(t_{ij}-1)+e_{ij}$$

or the quadratic regression

$$z_{ij}=a_i+b_i(t_{ij}-1)+c_i(t_{ij}-1)^2+e_{ij}$$

is postulated. In both regression equations the e_{ij} represent the deviations from the ideal relationship $(j=1,...,p_i)$; the time scale $(t_{ij}-1)$ was chosen in such a way that the theoretical scores at 1 year of follow-up are expressed by the a_i.

There are two different methods to work out these growth models:

Method A:

Lines or parabolas are fitted to the data using the least squares method. The resulting regression coefficients (a_i, b_i) in the case of a linear regression, and (a_i, b_i, c_i) in the case of a quadratic regression, can be used to characterize individual i; $i=1,...,n$. The coefficient a_i represents the z-score of an individual i after exactly 1 year of follow-up; the coefficient b_i represents the mean change of z-score per year at 1 year (i.e. deviation of the z-score as function of age); this change of z-score varies linearly as represented by the coefficient c_i. Note that the residuals e_{ij} can simply be read from a plot of the data and the corresponding line or parabola of closest fit. The a_i, b_i (c_i) and e_{ij} are thus more or less operationally defined as observable consequences of the least-squares method. The regression coefficients of a group of individuals can be assumed to be a sample out of some distribution characterizing the population that the individuals belong to.

However, since it was impossible to perform the measurement scheme exactly as planned, these sampling assumptions are open to criticism. Therefore, it seems preferable to regard a_i, b_i, (c_i) as estimates of certain unknown true values, corresponding to individual i, than as operationally defined characteristics. This brings us to the second method.

Method B:
Postulate that the z_{ij} observed satisfy the structure

$$z_{ij}=\alpha_i+\beta_i(t_{ij}-1)+\gamma_i(t_{ij}-1)^2+\varepsilon_{ij}$$

where the residuals ε_{ij} $(j=1,...,p_i)$ are independent and distributed as $N(0, \sigma^2)$. Note that the parameters α_i, β_i, γ_i and σ^2 are unknown and that the residuals ε_{ij} can not be observed. The regression coefficients a_i, b_i and c_i as defined under method A, are now regarded as estimates of the parameters α_i, β_i and γ_i. In this context it is natural to postulate that these unknown values $(\alpha_i, \beta_i, \gamma_i)$ are the outcome of a sample from a three dimensional distribution. In addition, trivariate normality can be postulated as well.

A theory concerning method B is described in detail in the thesis of Poortema.[42] A computer program for estimating (a_i, b_i, c_i) on the basis of method A as well as for evaluating method B was developed. Method B is obviously more sophisticated than method A and also more appropriate if deviations from the ideal scheme (such as the absence of data) cannot be avoided. However, we have used method A because the results of the two methods (A and B) do not differ appreciably if only few observations are absent and also because the mathematical elaboration of method B is rather complicated.

5.3 EXEMPLIFYING THE APPROACHES CHOSEN

In the following we will work out three approaches of analysing longitudinal data. Approach 1 is based on a linear regression model (straight line), approach 2 on a quadratic regression model (parabolic line) and approach 3 on 5 equidistant points of measurement (accepting deviations of 1 month from the scheduled time without interpolation). Approaches 1 and 2 are both based on method A as mentioned in §5.2. An example of the application of these three approaches to one individual is given in figure 5.1. The original data are presented in table 5.1. The least-squares regression line for this individual is given by

$$z=.38-.32(t-1)$$

while the parabola of closest fit is given by

$$z=.33-.31(t-1)+.12(t-1)^2.$$

In approach 1 each subject provides a value a_i for its z-score after exactly 1 year of follow-up (in the example $a_i=.38$) and a value b_i for its (mean) change of z-score per year at 1 year of follow-up (in the example $b_i=.32$); this change remains the same during the study. With approach 2 every subject also

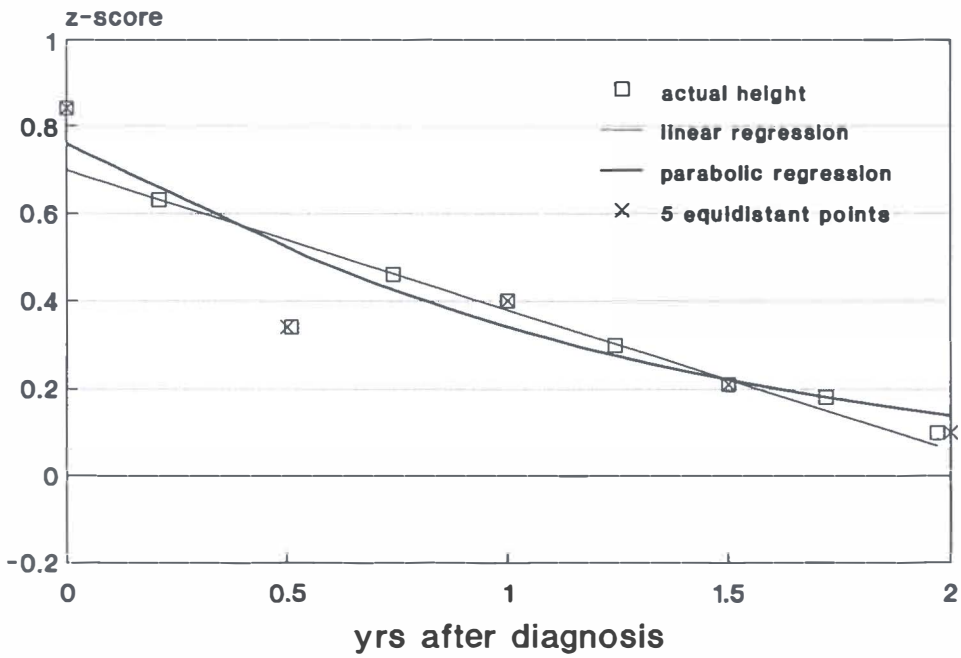


Figure 5.1 Analysis of height growth of the patient mentioned in table 5.1

Table 5.1 Example of the analysis of the height growth in a patient with ALL diagnosed at the age of 7.7 yrs.

age	yrs after diagnosis	height (cm)	z-score
7.75	0.0	135.1	.84
7.96	.21	135.2	.63
8.26	.51	135.4	.34
8.45	.74	137.4	.46
8.68	.97	138.4	.40
8.95	1.24	139.4	.30
9.20	1.49	140.3	.21
9.43	1.72	141.4	.18
9.68	1.97	142.4	.10

provides a value for a_i and b_i (in the example a_i=.33 and b_i=.31) as with approach 1, but the change of z-score varies linearly as given by the coefficient c_i (in the example c_i=.12); the change of z-score is equal to b_i at 1 year of follow-up and, of course, also if c_i=0. For healthy children the values a_i, b_i and c_i will be zero on average (for an individual child the values will be different), at least if the z-scores are correctly calculated using the appropriate reference study (chapter 3) and the child is measured correctly. A negative (positive) value of a_i indicates that that particular child's measurement result is smaller (larger) than the average for normal, healthy children. A negative (positive) value of b_i indicates that the growth rate of the child concerned is below (above) average.

The differences between the three approaches can be reviewed by comparing the values a_i obtained using either approach 1 or approach 2, with the

Table 5.2 Differences among 3 approaches to analyse anthropometric data obtained during a period of 2 years.

	z-score	(mean) change of z-score per year		
	at 1 yr	at $^1/_2$ yr	at 1 yr	at $1^1/_2$ yr
approach 1	a_i	b_i	b_i	b_i
approach 2	a_i	$b_i - {}^1/_2 c_i$	b_i	$b_i + {}^1/_2 c_i$
approach 3	z-score at	difference between z-scores at		
	t1	t1-t0	$t1^1/_2 - t^1/_2$	t2-t1

t denotes time at which measurement is performed (yr)

Table 5.3 Differences among 3 approaches to analyse height measurements obtained in one patient (table 5.1) during a period of 2 years.

	z-score	mean change of z-score per year		
	at 1 yr	at $^1/_2$ yr	at 1 yr	at $1^1/_2$ yr
approach 1	.38	-.32	-.32	-.32
approach 2	.33	-.43	-.31	-.19
approach 3	.40	-.44	-.13	-.30

actual z-score after 1 year of follow-up, obtained by using approach 3 (table 5.2). In addition, the estimated change per year in z-score at $^1/_2$, 1 and $1^1/_2$ year of follow-up, using approach 3, can be compared with the value b_i using approach 1 and with $b_i - {}^1/_2 c_i$, b_i and $b_i + {}^1/_2 c_i$ respectively using approach 2. The corresponding figures are given in table 5.3 for the individual studied before. Note that the results in this individual patient differ with the approach chosen. These differences are mainly caused by the measurement at 0.51 years after diagnosis. Considering that a measurement error with a deviation of e.g. 8 mm from the "true" value is possible (chapter 2) and can account for a deviation of .14 in z-score, the actual growth pattern displayed by this child, including the measurement at 0.51 years after diagnosis, may not be represented quite accurately by a linear or parabolic type of regression. A fast decrease in growth during the first months after diagnosis is not unlikely. Thus the models used in the statistical analysis should not be regarded without caution. On the other hand no analysis seems possible without some kind of approximation.

Because deviations from horizontal lines are our main interest, we prefer to use the approach which gives us the best information in this respect. Approach 1 (linear regression) is a good way to analyse growth which does not

show much shift in its change (i.e. deviation). A linear change of growth can, of course, not be infinite. Such an approach, however, may be appropriate during a period of 2 years. In approach 1 the change of growth is defined by just one coefficient (b_i) and that is why it can be analysed most easily. Approach 2 (quadratic regression) provides a good way to analyse growth if there is a gradual shift in its change. As the change of growth is here defined by two coefficients (b_i and c_i), it can still be analysed rather easily. Approach 3 (5 separate measurements) is a good way to analyse growth if the shift in its change is not gradual (or, more precisely, not constant) in such a way that, consequently, the quadratic regression is not a satisfactory model. Such deviations from the model may occur in patient groups, and in particular concern the growth of weight.

We have found the linear regression model used in approach 1 to be on the whole too simple. Hence, we prefer approach 2, while approach 3 will only be used for illustrative purposes.

5.4 ANALYSING LONGITUDINAL DATA OF HEALTHY CHILDREN

5.4.1. The anthropometric variables

As stated in §5.1, information concerning the longitudinal aspects of the growth of healthy children is needed, because the cross-sectional Oosterwolde reference study used[11] does not provide information relating to these aspects. The information required is obtained from a group of children from the Nijmegen mixed-longitudinal growth study.[17] This group consisted of 33 (originally 34, but one child was deleted because of atypicality) children, age and sex varying as described in §3.3. For each of these children the measurements that were used were obtained during the first 2 years. The children less than 9 years of age were measured every 6 months; the older children every 3 months.

Table 5.4 Mean and standard deviation of coefficient b_i and c_i in a group of 33 individuals of varying age and sex from the Nijmegen growth study.

anthropometric	value b_i		value c_i	
measurement	m	sd	m	sd
height	.05	.15	-.00	.12
weight	.01	.19	-.02	.14
W/H	-.06	.26	-.03	.26
arm circ.	-.01	.24	.01	.30
sitting height	.15*	.20	-.01	.17
head circ.	.03	.15	-.06	.18

W/H weight for height, circ., circumference.
* significantly different from zero ($p<.05$).

The average values of the coefficients b_i (mean change of z-score per year at t=1) and c_i (shift of the change of z-score) for this group of healthy children are presented in table 5.4, using approach 2 (§5.3). The mean change of z-score for height differs .05 from zero. Though this difference is not significant ($t=1.91$; $p>.05$), this

finding is not really satisfactory because the mean change should center around zero for healthy children since we are working with z-scores. It seems that part of the effect is caused by one rapidly growing individual with a coefficient b_i of .6 (see also figure 6.2); most children, however, will show an increase or decrease smaller than .6 per year as expressed by the standard deviation (.15; table 5.4). As for the sitting height the mean change of z-score is .15; this result is the only one significantly different from zero ($t=4.31$; $p<.05$). After removal of an outlier with a b_i of .9, the value for b_i is still significantly different from zero. This finding is peculiar. Differences in the technique of measurement between the Nijmegen growth study and the Oosterwolde reference study are unlikely to be the cause of this discrepancy. The secular trend is not likely to be responsible either, because this mainly influences the extremities.[43] The measurements of the other variables in the Nijmegen group show findings similar to the measurements of height.

The coefficients c_i are (as expected) in all measurements about zero; none was significantly higher or lower than zero.

5.4.2 Various groups of healthy children

The occurrence of a height growth spurt, especially at the time of puberty, might affect the interpretation of results based on z-scores calculated with a cross-sectional reference study. We therefore took, 6 extra groups of children from the Nijmegen study[17] in addition to the group studied in the preceding subsection, in order to investigate the possible influence of age and sex on z-scores of height. Data concerning sitting height were investigated as well, because b_i for the Nijmegen group studied in §5.4.1, differed significantly from zero. The groups consisted of 20 boys and 20 girls; 4, 8 and 12 years of age, respectively. The data obtained during 2 years of follow-up were analysed in the same way as those in the preceding subsection.

Table 5.5 Mean and standard deviation of coefficient b_i concerning height and sitting height in a group of 33 children of varying age and sex and in 6 groups of 20 boys and 20 girls respectively; aged 4, 8 and 12; all groups are from the Nijmegen growth study.

group	height		sitting height	
	m	sd	m	sd
various age/sex	.05	.15	.15*	.20
boys 4 yrs	-.03	.12	-.01	.20
boys 8 yrs	.04*	.08	.25*	.15
boys 12 yrs	.09	.25	-.01	.29
girls 4 yrs	.01	.20	.08	.19
girls 8 yrs	-.05*	.10	.08*	.15
girls 12 yrs	.08	.25	.06	.26

* significantly different from zero ($p<.05$)

Our findings concerning the coefficients b_i for height and sitting height are given in table 5.5. The findings concerning height in the specific groups of the Nijmegen growth study, are similar to those of the group of varying age and sex considered in §5.4.1. However, in the groups with children of the age of 8 we found b_i

values significantly different from zero (note that the corresponding standard deviations are smaller than for the other age groups). The average b_i value for children of the age of 12 is the largest and so is the standard deviation, as was to be expected.

The coefficients b_i for sitting height (table 5.5) show more variation than those for height. Again the average b_i in both groups of 8-year-old children, are significantly different from zero; again the corresponding standard deviations are smaller than those in the other age groups.

We tried to account for our finding that the b_i for height and sitting height were different from zero for children 8 years of age. Neither a comparison of the growth curves of boys and girls with each other,[11] nor a comparison of the growth curves of Oosterwolde reference study[11] with those of the Nijmegen growth study,[17] provided an explanation. The finding is therefore interpreted neither as an indication that the Oosterwolde reference study is unreliable, nor as an indication that our approach is invalid, but merely as an irregularity.

5.5 CONCLUSIONS

It can be concluded from the results recorded in §5.4 that it is valid procedure to collect growth data, over a period of 2 years, from a group of individuals and compare those data with similar data from another group by transformation of the measurements into z-scores on the basis of the Oosterwolde reference study.[11] It should be noted, however, that the groups from the Nijmegen growth study cover only the age range of 4-14 and that the findings concerning the sitting height could not be explained sufficiently.

Most of the data will be analysed using approach 2 (§5.3). This implies that the results of the analyses of patient groups can be tested for atypicality in three different ways.

In the first place, the results found in the different patient groups can be compared with the Oosterwolde reference study by comparison of the average of coefficients a_i, b_i and c_i for a patient group with zero, applying Student's t-test. If the null hypothesis is rejected then this indicates that a difference exists between the group considered and the Oosterwolde reference population. Secondly, if one does not want to rely on this reference study,[11] then one can alternatively apply the two-sample t-test instead, to compare a patient group with one of the groups from the Nijmegen growth study,[17] in particular the group of §5.4.1, with individuals of varying age and sex. And lastly, patient groups can be compared with each other, also applying the two-sample t-test.

CHAPTER 6

GROWTH OF CHILDREN WITH CANCER

6.1 INTRODUCTION

It has been known since 1975 that height retardation may occur in children treated for a brain tumor, even if the tumor does not directly involve the hypothalamic pituitary region.[9,10,44,45] This height retardation is usually associated with growth hormone deficiency[10,45,46] and/or other pituitary deficiencies caused by therapeutic (>25-30 Gy) cranial irradiation.

Pinkel was the first to publish on height retardation in children with ALL.[47] Since then many authors have reported height retardation of children treated for acute lymphoblastic leukaemia (ALL).[3,22,26,48-55] The relative retardation in patients whose treatment (including cranial irradation) had been completed was less than in children with a brain tumor and was estimated to be about 0.5 standard deviation unit.[3,26,48,51-55] Most investigators assume that this effect is treatment-related; cranial irradiation is particularly mentioned, although the radiation doses applied in ALL are less (18-24 Gy) than in patients with a brain tumor. It is thought that this central nervous system treatment affects the (pulsatile) growth hormone secretion in such a way that growth is impaired.[4-6,22,48,52,56-61] However, other findings suggest that chemotherapy contributes to this growth impairment.[54,62] The growth disorders secondary to cranial irradiation applied for brain tumors and ALL, have recently been reviewed.[63] Controversial findings are reported for children with ALL treated without cranial irradiation. Some investigators have found height retardation,[55,64] though others have not.[7,65-67]

In addition to the consequences of cranial irradiation and chemotherapy, local irradiation may affect growth; for example spinal irradiation of more than 20 Gy in children with a brain tumor, ALL, M. Hodgkin, neuroblastoma or Wilms' tumor, may cause growth impairment of the spine, resulting in a reduced sitting height.[68-72]

Catch-up growth is often seen in children after a serious disease.[73,74] Such a catch-up growth should also occur in children with cancer after reaching complete remission, or, if a catch-up growth occurred before, after completion of therapy, unless the ability to catch up is lost due to the treatment. Most data regarding catch-up growth come from patients with ALL; most investigators have found a considerable catch-up growth in these children,[7,26,54,55,75] but not all.[3,52]

As mentioned above some aspects concerning growth are known, but controversies still exist, especially with regard to the influence of chemotherapy and cranial irradiation in doses up to 24 Gy. Moreover little knowledge exists about anthropometric measurements other than height, weight and sitting height.

The main purpose of our growth study was to investigate (1) whether growth retardation in our patients does occur and is similar to that mentioned in the literature, (2) whether differences exist among patients treated with different treatment regimes of which some include irradiation, and (3) whether catch-up growth occurs after completion of therapy. The measurements were not restricted to height, weight and sitting height; head circumference, upper-arm circumference and armspan were investigated as well.

6.2 PATIENTS AND METHODS

Between March 1982 and April 1986, 130 children with cancer entered our growth study; for various reasons the data of only 79 children could be analysed (see §1.4). These patients were stratified according to table 1.3. The groups 1-6 were followed from diagnosis and the groups 7-8 from completion of therapy. Additional information on brain tumor patients (group 1) is provided in table 6.1 and for the treatment regimes used in ALL patients (groups 2-4) in table 6.2.

Possible factors influencing growth during cancer treatment, such as tube feeding and infections are given in table 6.3. The need for tube feeding was small in group 4, and infections occurred rarely in group 1. No other notable differences were found.

Table 6.1 Characteristics of 9 patients with a brain tumor (group 1).

#	sex	age (yrs)	diagnosis	radiation Gy hypoth/spinal	hormonal substitution
involving hypothalamic pituitary region:					
1	F	3.5	craniopharyngioma	54/-	TSH/ACTH/ADH
2	F	8.4	craniopharyngioma	50/-	TSH/ACTH
3	F	8.5	glioma	60/30	TSH/ACTH/ADH
4	F	9.5	dysgerminoma	30/30	TSH/ADH
5	F	11.7	optic glioma	50/-	TSH/ACTH/ADH
not involving hypothalamic pituitary region:					
6	M	4.2	ependymoma	40/30	-
7	M	9.9	medulloblastoma	35/35	-
8	M	12.5	medulloblastoma	30/30	-
9	M	14.7	medulloblastoma	35/35	-

Table 6.2 Differences in the treatment regimes between group 2, 3 and 4 (the number of patients who were treated is mentioned between brackets).

	group 2	group 3	group 4
indication	high risk	standard	standard
CNS-treatment:			
-i.t. chemotherapy	+ (5)/ ++ (2)	+	++
-cranial irradiation	24 Gy (6)/ 18 Gy (1)	24 Gy (4)/ 18 Gy (9)	-
-high dose MTX	-	-	+
consolidation	ara-c/ cyclophosphamide	-	-
corticosteroids:			
-prednisone 40 mg/m^2	(5)	all	-
-dexamethasone 6 mg/m^2	(2)	-	all

CNS, central nervous system; i.t., intrathecal; MTX, methotrexate.

Table 6.3 Use of tube feeding (percent of study period) and number of infections during the study, requiring intravenous antibiotics.

group	tube feeding (%) (mean)	infections
1	15	.3
2	32	2.9
3	33	1.8
4	9	1.4
5	32	2.2
6	23	1.8

Anthropometric measurements included height, weight, weight for height, upper-arm circumference, sitting height, armspan and head circumference. The measurements were performed according to the guidelines of Cameron[12] (see appendix). The measurements were scheduled to be performed at diagnosis and thereafter every 3 months, up to 2 years after diagnosis (groups 1-6) or up to 2 years after completion of therapy (groups 7 and 8). Of the scheduled height measurements 80-91% could be performed (table 1.6) in the evaluable patients.

Physical properties resulting from differences in age and sex were eliminated by calculating z-scores (chapter 3). This enabled us to compare the patient groups with one another. Reference values for these calculations were derived from the Oosterwolde study.[11] The methods for analysis of series of z-scores as well as the results found in a group of children from the Nijmegen mixed-longitudinal study[17] are discussed in chapter 5. The approach ultimately chosen was based on the assumption that series of z-scores for any particular patient, obtained during a period of 2 years, can be approximated (using least squares) by a parabola. The approximation is given by

$$z_{ij}=a_i+b_i(t_{ij}-1)+c_i(t_{ij}-1)^2+e_{ij}$$

(see §5.2). Every subject, consequently, provides a value a_i for its z-score after 1 year of follow-up and a value b_i for its (mean) change of z-score per year, at

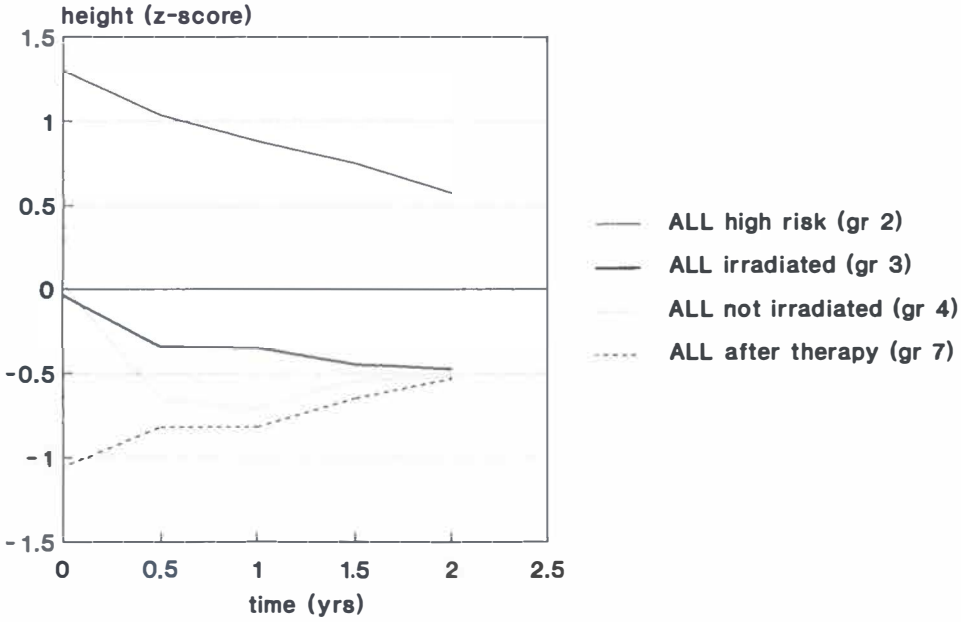
1 year of follow-up; this change of z-score differs continuously as defined by coefficient c_i.

6.3 RESULTS

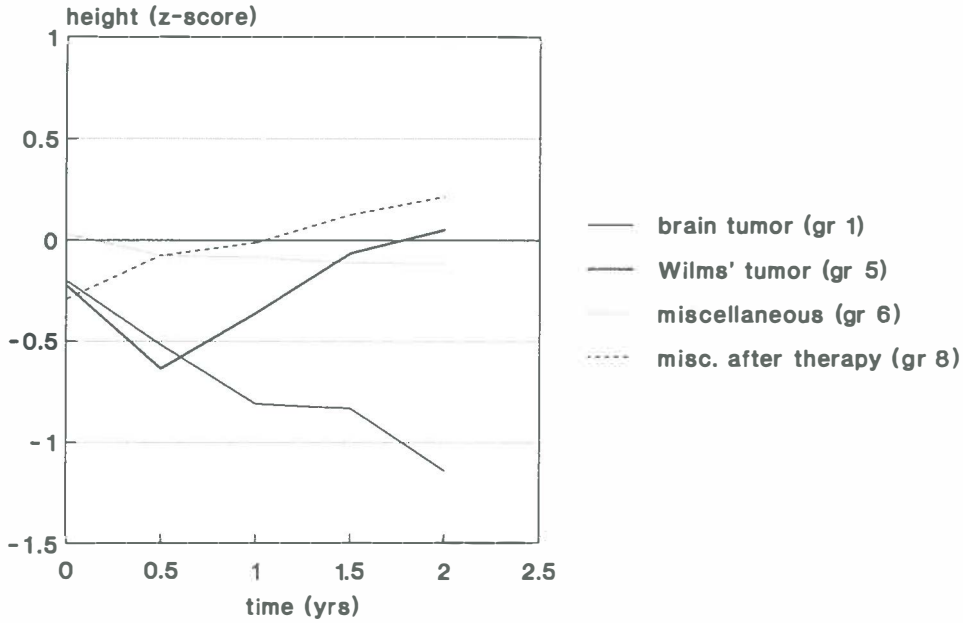
In this section we present in detail our findings for each anthropometric variable separately. In addition, the findings of all the variables in ALL patients are given in §6.3.8. In the last subsection the relationship between height and sitting height is presented of those patients who received spinal irradiation.

6.3.1 Height

The mean height expressed as z-scores during the study period in the various patient groups is presented in figures 6.1a and 6.1b. Height is retarded most in brain tumor patients (group 1). This retardation was progressive during the whole study period. The height retardation of ALL patients during therapy (groups 2-4) was maximal during the first half year after diagnosis. The apparent tallness of children with an high risk ALL is caused by one very tall patient (figure 4.1). The patients with a Wilms' tumor (group 5) display a height retardation only during the first half year after diagnosis; they show a notable catch-up growth starting at already 6 months after diagnosis. No



Figures 6.1a Mean height at 1/2, 1, 1 1/2 and 2 years of follow-up (z-score), stratification according to table 1.3.



Figures 6.1b Mean height at 1/2, 1, 1 1/2 and 2 years of follow-up (z-score); stratification according to table 1.3.

disturbance of height growth was observed in the patients treated with high doses of MTX and/or cyclophosphamide (group 6). It should be noted that these patients have a high median age in comparison with the other patients investigated during therapy (table 1.5). A catch-up growth was found in the patients with ALL investigated after completion of therapy (group 7). Their mean z-score for height was at the start of the study <-1, and reached the level of almost -.5 two years later. An enhanced height growth was also noticed in the patients after completing treatment with various intensive chemotherapy regimes (group 8), though in the patients treated similarly (group 6), no retardation during treatment was found.

The values of coefficients b_i, representing the mean change of height per year (expressed as z-score) for each individual i at 1 year of follow-up, are presented in figure 6.2. One patient in group 1 (with a craniopharyngioma) has an increase in height of >1.0 SD and one patient in group 4 has a decrease in height of >1.5 SD.

The mean of the coefficients b_i are presented in table 6.4 after removal of the two outliers. A negative average value of coefficient b_i, significantly different from zero, was found in groups 1-4 and a statistically significant positive value in groups 5, 7 and 8. The significance of the negative values becomes even greater when we compare these values with those from the Nijmegen growth study, while the significance of the negative values is considerably less,

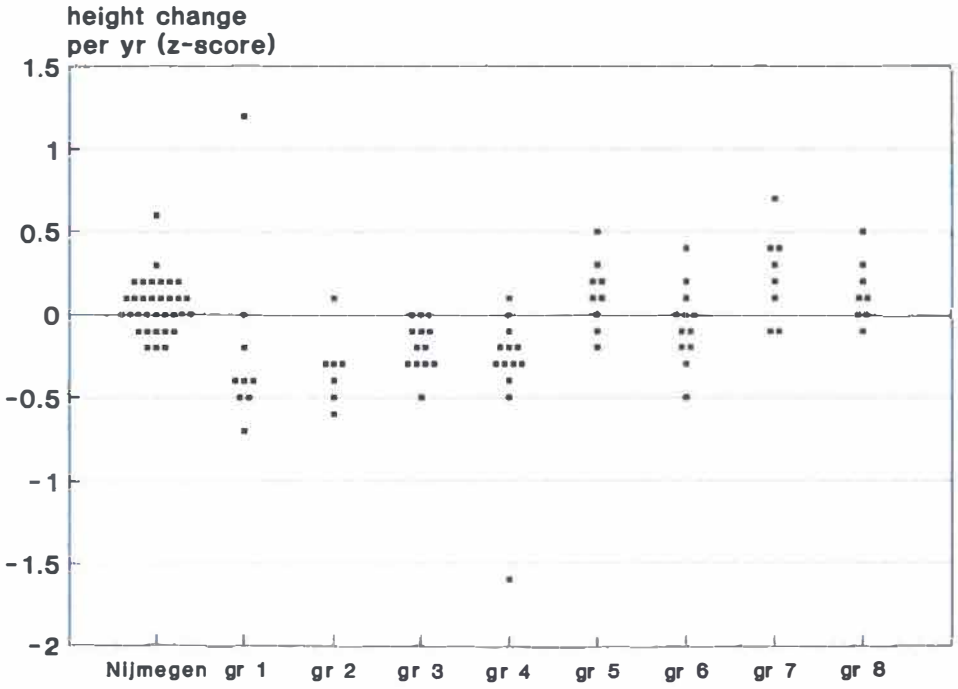


Figure 6.2 Change of height per year per individual at 1 year of follow-up (z-score), i.e. coefficient b_i; stratification according to table 1.3.

Table 6.4 Coefficient b_i and c_i for height in a group from the Nijmegen growth study and 8 patient groups (mean and sd).

group	b_i		c_i	
	m	sd	m	sd
Nijmegen	.05	.15	.00	.12
1#	-.36*	.22	.10	.21
2	-.32*	.18	.09	.31
3	-.18*	.16	.16*	.14
4#	-.22*	.18	.04	.15
5	.20*	.23	.25*	.27
6	.06	.22	.05	.21
7	.24*	.27	-.11*	.11
8$	.22*	.16	.04	.15

# one patient not included in the analysis for being an outlier
$ three patients not included in the analysis for having an endoprothesis in one of the legs
* significantly different from zero ($p < .05$)

or even absent, in groups 5 and 7. The mean value of the b_i of the patients in group 6 is not significantly different from zero. The growth retardation (as represented by coefficient b_i) in groups 1-4 is in comparison with the patients of group 6 significant in groups 1, 2 and 4.

The mean value of the coefficients c_i (table 6.4) is significantly different from zero in groups 3, 5 and 7. That this value in groups 3 and 5 is higher than zero, indicates that the height retardation in these groups is maximal in the first half of the study, which is also shown by figure 6.1. In group 4 a positive mean value of c_i was also expected (given the data in figure 6.1), but was not found; appar-

ently the outlier (removed from the computations) dominated figure 6.1. That the value c_i in group 7 is lower than zero, indicates that the catch-up in this group is maximal in the first period after completion of the ALL treatment. The values c_i in the other groups are not significantly different from zero.

6.3.2 Weight

The mean change of weight growth at 1 year of follow-up (value b_i) was above zero in almost all patient groups (table 6.5), though in none significantly different from zero. Note that the standard deviations of coefficient b_i and c_i are larger than in table 6.4 where height was considered, which indicates a larger variation of weight-growth change than of height-growth change.

Table 6.5 Coefficient b_i and c_i for weight in a group from the Nijmegen growth study and 8 patient groups (mean and sd).

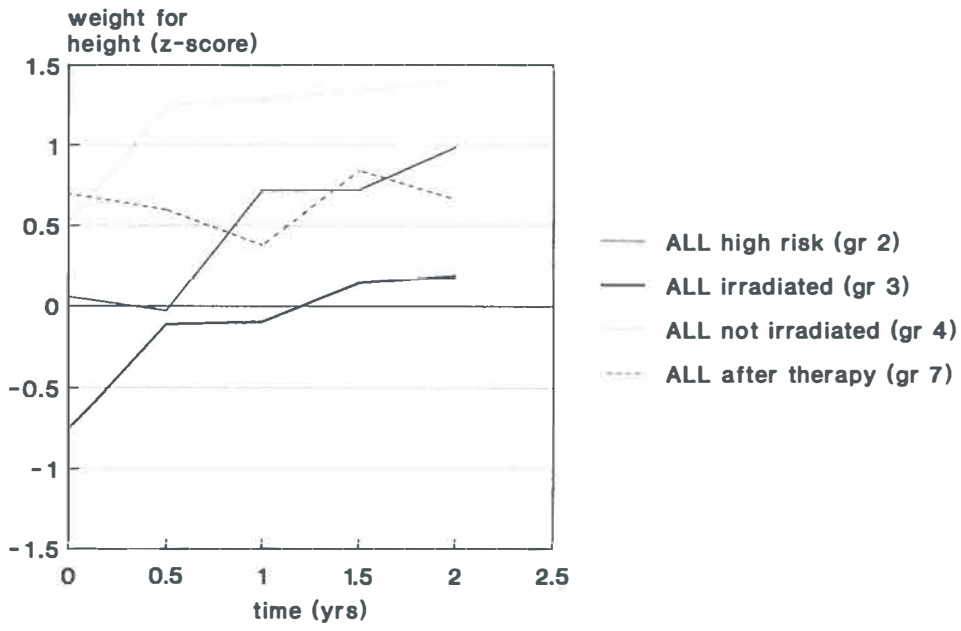
group	b_i		c_i	
	m	sd	m	sd
Nijmegen	.01	.19	-.02	.14
1#	-.10	.45	.17	.66
2	.20	.50	-.18	.49
3	.14	.33	-.18	.34
4#	-.03	.55	-.22	.42
5#	.26	.43	-.45	.69
6	.16	.32	-.10	.41
7	.20	.39	-.05	.40
8$	.39	.47	.02	.22

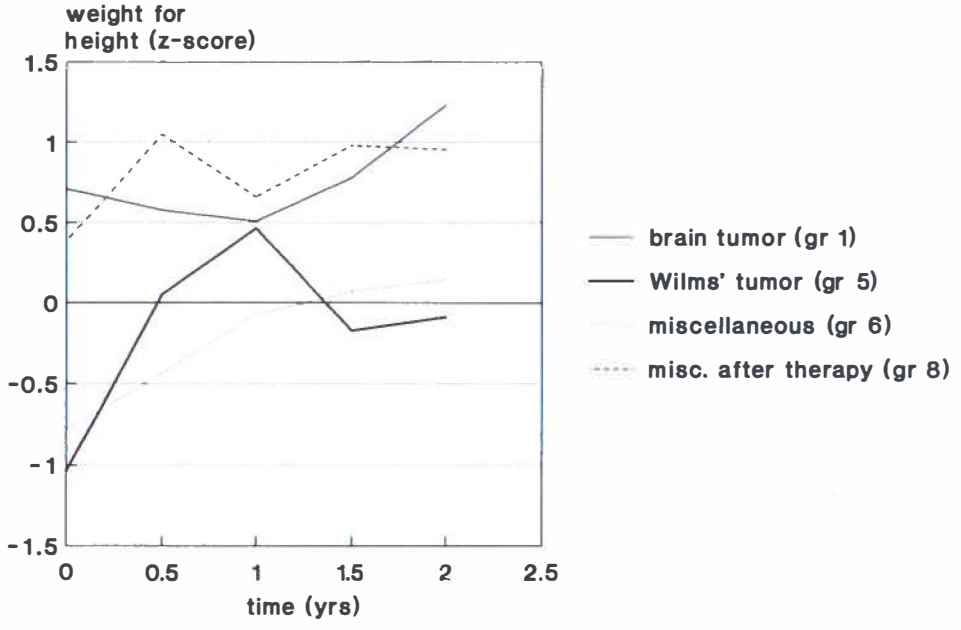
see table 6.4 for notes

6.3.3 Weight for height

The mean weight corrected for height found in the various patient groups at diagnosis and at intervals of 6 months afterwards, is shown in the figures 6.3a and 6.3b. In general, in all groups the increase in weight is more than average. This increase in weight is most clear in Wilms' tumor patients (group 5); they have a low mean weight for height at diagnosis and regain weight in the first 6 months after diagnosis. An increase in weight of about 1 standard deviation during the follow-up period is found in the groups with ALL patients during treatment (groups 2-4); this leads to a z-score of almost 1.5 at the end of follow-up for the patients of group 4.

The mean values of the coefficients b_i are given in table 6.6. The results in groups 3 and 4 are significantly different from zero. The results in groups 2 and 6 are only significantly different in comparison with the Nijmegen growth study. No significant differences concerning the values b_i could be established among the various patient groups. The mean values of coefficient c_i are significantly different from zero in groups 3 and 5. This indicates in both groups that the increase in weight is at its highest in the first part of the study. The mean value of the coefficients c_i in group 5 is very high, as could be expected from figure 6.3b.





Figures 6.3a and 6.3b Mean weight for height at 1/2, 1, 1 1/2 and 2 years of follow-up (z-score); stratification according to table 1.3.

Table 6.6 Coefficient b_i and c_i concerning weight for height in a group from the Nijmegen growth study and 8 patient groups (mean and sd)

group	b_i		c_i	
	m	sd	m	sd
Nijmegen	-.06	.26	-.03	.26
1#	.22	.57	.22	1.11
2	.43	.61	-.29	.61
3	.46*	.44	-.33*	.49
4#	.33*	.45	-.35	.77
5#	.13	.62	-.94*	.76
6	.35	.63	-.22	.61
7	.01	.44	.06	.75
8$	.32	.52	.00	.29

see table 6.4 for notes.

Table 6.7 Coefficient b_i and c_i for upper-arm circumference in a group from the Nijmegen growth study and 8 patient groups (mean and sd)

group	b_i		c_i	
	m	sd	m	sd
Nijmegen	-.01	.24	.01	.30
1#	-.02	.78	.13	.81
2	.60*	.32	-.38*	.43
3	.64*	.43	-.31	.61
4#	.23	.69	-.81*	.60
5#	.49	.76	-.70	1.08
6	.43*	.50	-.32	.68
7	.36*	.33	.12	.67
8$	.48	.59	.16	.38

see table 6.4 for notes

6.3.4 Upper-arm circumference

The mean values of the coefficient b_i concerning upper-arm circumference (table 6.7) on the whole parallel the results of weight for height (table 6.6). A growth significantly above normal is found in groups 2, 3, 6 and 7. Note that a large difference exists between the ALL patients of groups 3 and 4; this difference, however, is of no real statistical significance (t-value 1.82; p>.05).

Table 6.8 Coefficient b_i and c_i for sitting height in a group from the Nijmegen growth study and 8 patient groups (mean and sd).

group	b_i		c_i	
	m	sd	m	sd
Nijmegen	.15*	.20	-.01	.17
1#	-.37*+	.27	-.02	.39
2	-.27*+	.31	-.24*	.27
3	-.09+	.31	-.01	.28
4#	-.20+	.40	-.10	.24
5#	.12	.19	-.13	.70
6	.08	.21	-.15	.41
7	.39*	.32	-.21*	.18
8$	.29	.35	-.14	.28

+ significantly different from control group (p<.05)
see table 6.4 for additional notes

6.3.5 Sitting height

Sitting height (table 6.8) on the whole parallels height. The mean value of the coefficients b_i for sitting height is significantly different from the Oosterwolde reference population in groups 1, 2 and 7. However, the mean value of b_i for sitting height of the Nijmegen growth study is also significantly different from zero. Significantly different results were found in the groups 1-4, when the patients' results were compared with this Nijmegen group. Comparison of the results of groups 1-4 with those of group 6, revealed a significantly different growth in groups 1, 2 and 4. Curiously

enough, the coefficient c_i has a negative sign in group 2 while coefficient b_i is also negative; this may indicate a progressive sitting-height retardation towards the end of the follow-up. The negative sign of coefficient c_i in group 7 indicates that a catch-up growth of sitting height mainly takes place in the first part of the study.

Table 6.9 Coefficient b_i and c_i for armspan in 8 patient groups (mean and sd).

group	b_i		c_i	
	m	sd	m	sd
1#	-.46*	.29	.09	.20
2	-.48*	.49	.20*	.15
3	-.40*	.62	-.08	.52
4#	-.36*	.38	-.02	.25
5#	-.46*	.53	.10	.57
6	.15*	.16	.10	.30
7	.16	.37	-.29	.48
8$	-.02	.27	.04	.22

see table 6.4 for notes.

Table 6.10 Coefficient b_i and c_i for head circumference in group from Nijmegen growth study and 8 patient groups (mean and sd).

group	b_i		c_i	
	m	sd	m	sd
Nijmegen	.03	.15	-.06	.18
1	-.08	.18	-.06	.41
2	-.04	.29	-.09	.44
3	-.08	.18	.12	.23
4#	-.04	.27	-.20*	.33
5#	.40*	.23	.05	.37
6	.27*	.36	.13	.35
7	-.03	.06	-.09	.13
8$	.08	.27	-.21	.26

see table 6.4 for notes.

6.3.6 Armspan

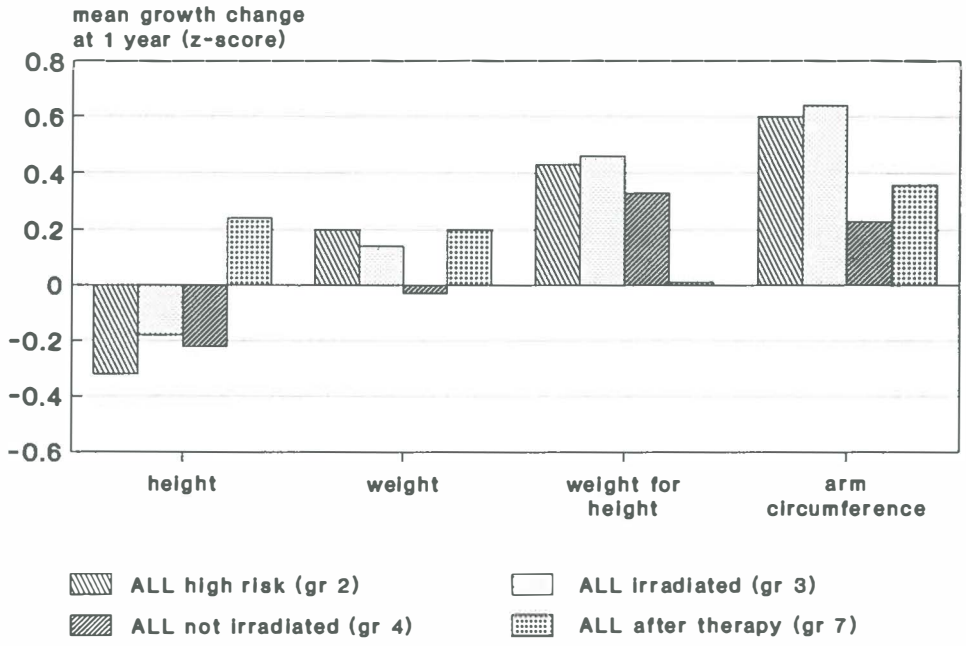
The growth of armspan in groups 1-5 is retarded (table 6.9). This finding is similar to the results concerning height (table 6.4). Note that armspan at diagnosis was rather large in patients with leukaemia or solid tumors (table 4.4). Unfortunately armspan values from the Nijmegen growth study are not available. It is obvious that the results in group 7 are significantly different from the results in groups 2-4, which is indicative of catch-up growth occurring.

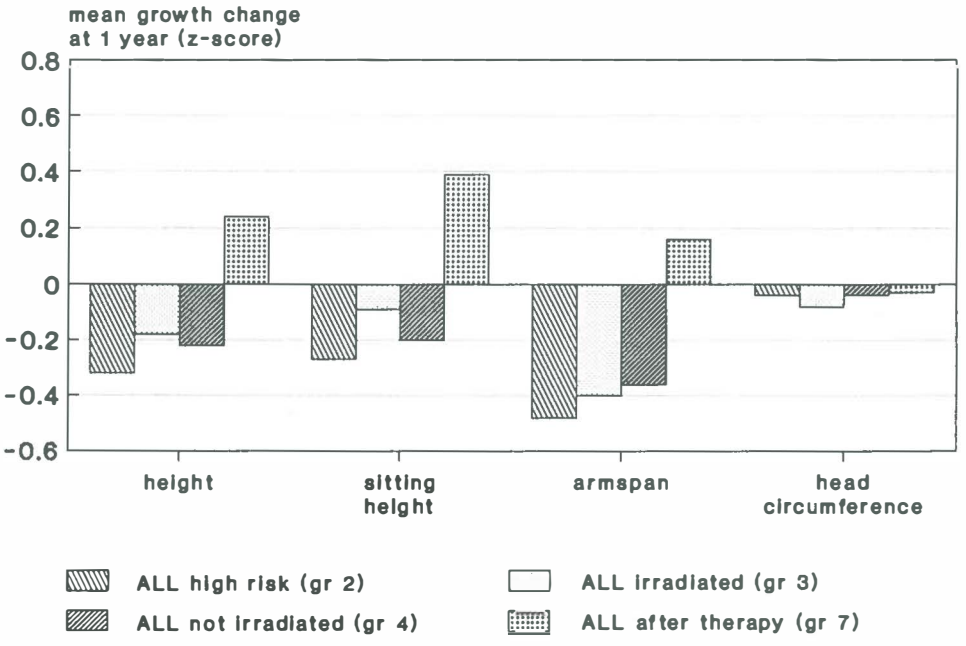
6.3.7 Head circumference

The growth of the head was not significantly different from the Oosterwolde reference population in groups 1-4 (table 6.10). However, a growth above normal was found in groups 5 and 6.

6.3.8 Results in ALL patients

The mean values of the coefficients b_i found in groups 2-4 and 7, concerning the various anthropometric variables discussed before, are shown in figures 6.4a and 6.4b. Note that during and after therapy weight, weight for height and upper-arm circumference show an enhanced growth in comparison with the Oosterwolde reference population. The linear measurements (height, sitting height and armspan) are retarded in the groups 2-4 and show catch-up growth after cessation of treatment (group 7). The growth of head circumference shows no abnormalities during or after treatment.





Figures 6.4a and 6.4b Mean change per year of various anthropometric variables at 1 year of follow-up (coefficient b) in 4 groups with ALL patients, stratification according to table 1.3.

Table 6.11 Difference between b_i for armspan and b_i for sitting height respectively height in three ALL patient groups (mean and sd).

group	b_i		c_i	
	m	sd	m	sd
2	-.17	.43	-.22	.61
3	-.20	.67	-.26	.58
4	-.13	.24	-.21	.35
2-4	-.17	.48	-.23*	.49

* significantly different from zero ($p < .05$).

The growth retardation of armspan in groups 2-4 seems larger than for height or sitting height, suggesting a possible difference of growth retardation between long bones and the spine. We therefore decided to compare the b_i for armspan and the b_i for height or sitting height of each individual i. The results are given in table 6.11. A significant finding only emerged in the case of the difference between armspan and sitting height when we combined all three groups. No significant correlation could be found between age and the retardation of height, sitting height or armspan.

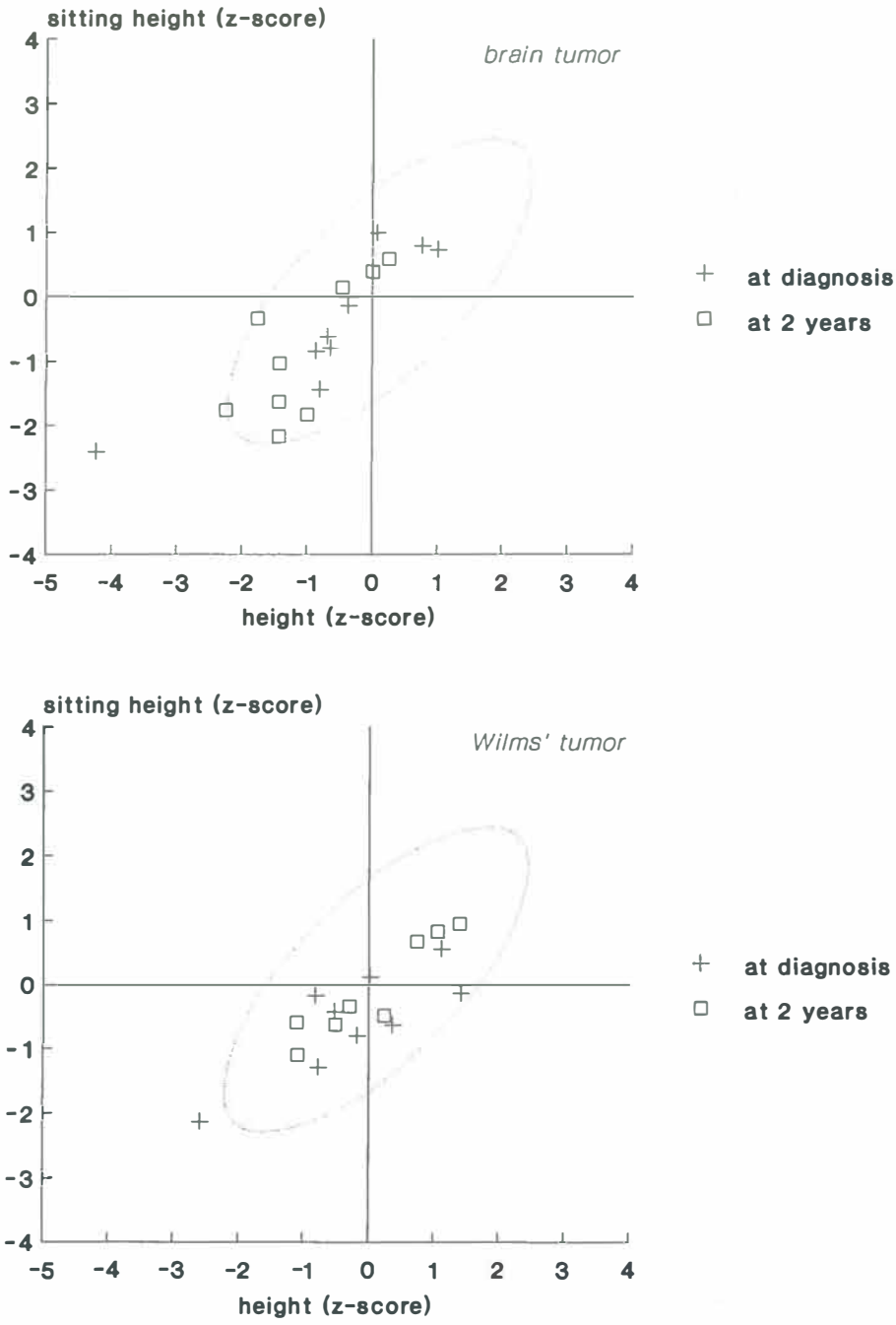
6.3.9 Relationship between height and sitting height

Since local irradiation is known to cause growth retardation, the relationship between height and sitting height at diagnosis and at the end of follow-up was investigated in patients whose treatment included spinal irradiation. The data are presented in figure 6.5a for brain tumor patients (group 1) and 6.5b for Wilms' tumor patients (group 5). At diagnosis one patient with a brain tumor (craniopharyngioma) fell outside the 95% confidence region for healthy children; she seemed to have normal proportions but had a low height and sitting height; at the end of the study she appeared to have caught up in both height and sitting height, and fell within the normal region. The other patients showed in general a shift to the lower left part of the figure, which indicates retardation of both variables, without, however, leaving the normal region.

One of the Wilms' tumor patients showed a relationship between height and sitting height outside the 95% confidence region; none, however, at a follow-up of 2 years.

6.4 DISCUSSION

The main aim of our study was to look for differences in growth between several patient groups concerning various anthropometric variables. Moreover the growth in patients was compared with a reference population (Oosterwolde) and a group of healthy children (Nijmegen).



Figures 6.5a and 6.5b Relationship between height and sitting height in patients with a brain tumor (a) or a Wilms' tumor (b), at diagnosis and 2 years later. The oval area represents the 95% confidence region in the reference population.[11]

6.4.1 Height

Height retardation (§6.3.1) during treatment was predominant in brain tumor patients (group 1) and patients with high risk leukaemia (group 2). The results for the latter group, however, were not significantly different from other ALL patients (groups 3 and 4). A mean height impairment of .72 standard deviation unit was observed in 8 out of 9 children with a brain tumor, which confirmed and extended the cross-sectional[9,10,44,45] and longitudinal[46,70,76-78] study results of other investigators. This height impairment adds to the height retardation already existing at diagnosis in some of these patients (chapter 4). Only one child (with a craniopharyngioma; no 1, table 6.1) showed an accelerated height growth. Such an unexpected catch-up growth has also been observed by others.[79-83] The retardation of height in children with ALL averaged between .64 and .36 standard deviation unit (depending on the group considered) during the 2 years of treatment. The extent of height retardation is consistent with previous reports.[3,26,48,51-55] Most investigators noticed the greatest reduction in height growth during the first year of treatment for ALL.[3,22,26,50,54,55] Our data provide further evidence for this (figure 6.1a); in addition, coefficient c_1 was significantly above zero in group 3 (table 6.4). The Wilms' tumor patients (group 5) showed a catch-up growth as early as from 6 months after diagnosis. Patients of group 6 showed no significant height retardation at all.

A likely explanation for the height retardation in brain tumor patients is growth hormone (GH) deficiency and/or gonadal dysfunction due to tumor growth in the hypothalamo-pituitary region, or surgical and/or radiation therapy.[10,45,46,76,78,84] Spinal irradiation may further increase this height retardation (see below, §6.4.3). We found height retardation not only in children with a tumor of the hypothalamo-pituitary region, but in other patients as well. Impaired pubertal development was noted in three patients; two of them had a tumor outside the hypothalamo-pituitary region (chapter 8). The cause of the height retardation in patients with ALL is also thought to be cranial irradiation, though controversies exist on this point (see §6.1). Some authors even reported on a differential effect on height retardation of 18 and 24 Gy cranial irradiation; such an effect on height growth was found by some[54,75], but not by others.[67] Most patients in group 2 (6 out of 7) received 24 Gy and most patients in group 3 (9 out of 13) 18 Gy cranial irradiation. However, we found no significant difference in height retardation between groups 2 and 3. A possible explanation is that differences in fractionation and duration of the cranial irradiation are more important than the radiation dose itself.[4] The patients in our study who received 24 Gy cranial irradiation were usually treated in 15 fractions during a total period of 3 weeks. Fewer fractions are considered to increase the risk of the occurrence of growth hormone deficiency and concomitant growth retardation.[85] An additional explanation may be that a follow-up of 2 years is too short to establish differences among different groups.

Chemotherapy may be an additional cause of height retardation; indeed, it may even be a more decisive element than the influence of cranial irradiation. On the one hand we found in ALL patients treated only with chemotherapy (including corticosteroids; group 4) a height impairment similar to the impairment in children whose treatment included cranial irradiation (group 3). This finding corresponds with the findings in some reports[55,64], while it differs from the findings in others.[7,65-67] On the other hand no significant difference in height retardation was found between the patients of group 2 who received an additional course of chemotherapy (consolidation; table 6.2) and the patients of group 3. Moreover, despite the chemotherapy given to the patients of group 5, a catch-up growth was possible; nor did chemotherapy given to patients of group 6 impair height growth.[3,71] However, some patients of group 6 are rather old and therefore may be less sensitive to growth impairment. The height loss observed in group 5 during the first 6 months after diagnosis, might be caused by the initial treatment (chemotherapy and radiotherapy); however, a more likely explanation is the influence of disease itself and/or the laparotomy at diagnosis. It follows from the above that the observed height retardation in group 4 must mainly be due to the corticosteroid treatment (dexamethasone), while an additional effect of cytostatic treatment may exist. It is well-known that there is a connection between corticosteroid treatment and growth retardation,[86] even when the steroids are given intermittently, as e.g. in the case of asthmatic children.[87] In addition, a drug-induced diminished somatomedin production and cartilage response to somatomedin have been reported.[88]

In ALL patients a catch-up growth was found as was to be expected on the basis of the literature.[7,26,54,55,75] This catch-up growth after treatment is of the same order as the retardation during treatment. Thus a normal adult height can be expected. A catch-up growth was also found in the patients of group 8, though no impaired height growth was established in the patients of group 6. Differences in patients (age), diagnoses and therapies may be responsible for this discrepancy, although there were some common aspects concerning the chemotherapy (table 1.3).

6.4.2 Weight, weight for height and upper-arm circumference

With respect to anthropometric variables reflecting the nutritional status (weight, weight for height and upper-arm circumference), the standard deviation of the mean value of the b_i was large in many patient groups, which indicates a large variation. Nevertheless, in ALL patients (groups 2-4 and 7) and in the patients of group 6, one or more of the mean values b_i for these anthropometric variables were significantly above zero. The results of Wilms' tumor patients (group 5) are not significantly different from those of the Nijmegen growth study, because most increase in weight occurred already in the first 6 months of the study (see figure 6.3b and mean c_i, table 6.6). One patient with

a brain tumor (no 3, table 6.1) showed a large weight gain in combination with a retarded height growth, resulting in excessive growth of weight for height; she was omitted from the calculations; the other patients of group 1 showed no significant change in their nutritional status.

An accelerated weight growth in ALL patients has been noted before.[50,67,89] Part of the explanation can be found in the additional tube feeding that was given to those patients who were unable to maintain their weight. In addition, corticosteroids can cause excessive weight gain in these patients;[50] the difference in the glucocorticoid effect between dexamethasone (6 mg/m^2) and prednisone (40 mg/m^2) may explain why the children of group 4 needed less tube feeding than children of group 3. Psychological factors have also been reported to influence weight, which may help to explain why the weight gain tends to continue after cessation of treatment.[50] Similar observations were made with our patients (group 7). Our data do not provide evidence for considering cranial irradiation as a major adverse factor, in contrast to other investigations.[89]

The weight gain found in the patients of groups 5 and 6 is probably a compensation of weight loss due to the disease before treatment was started. It is a well-known fact that the nutritional status of patients with a solid tumor at diagnosis can be poor (see figure 6.3b and chapter 4).

6.4.3 Sitting height and armspan

The growth of sitting height and armspan was significantly below the growth in the Nijmegen growth study and the Oosterwolde reference population in groups 1-4. The growth of sitting height was significantly above normal in group 7. The growth of sitting height and armspan parallel the height growth in all patient groups, except in group 5.

The mean values b_i concerning armspan of ALL patients during treatment (groups 2-4) are lower than the mean values b_i concerning height and sitting height, which suggests that the growth of arms and legs (long bones) are more affected in these patients than e.g. the growth of the spine. The indication of such disproportional growth retardation could only be confirmed for the difference between armspan and sitting height through combining groups 2-4. We have come to the conclusion that this effect is caused by the chemotherapy including corticosteroids, because (again) no differences existed between patients treated with and without cranial irradiation. We could not establish a significant correlation between age and growth retardation. It is not known to us whether any reports exist that mention growth retardation of extremities larger than that of the spine.

Six out of a total of 9 patients of group 1 and 6 out of a total of 9 patients of group 5 received some irradiation which included the spine. A disturbed relationship between height and sitting height, however, could not be establish-

ed in them during the 2 years of study (figure 6.5). Disproportional reduced sitting height in patients with a brain tumor has been reported,[90] but mostly after more time had elapsed since spinal irradiation[70,72] or after substitution with growth hormone had taken place.[91] Reduced sitting height has also been found in Wilms' tumor patients.[71] Our patients, however, received lower doses of irradiation than those mentioned in that publication.

6.4.4 Head circumference

Head growth was not significantly impaired in any of the patient groups, though the treatment included cranial irradiation with the brain tumor patients and with the ALL patients of groups 2, 3 and 7. The radiation dose of 18-24 Gy with these leukaemic patients is probably too low to cause stunted head growth, although a dose of 30 Gy with the patients of group 1 could do so. It is important to realize that most of the head growth occurs during early childhood and that impairment later is difficult to establish within 2 years after the irradiation. There has been a report, however, of a reduced head circumference at about 9 years after cranial irradiation.[92]

The accelerated growth of the head circumference in groups 5 and 6 cannot be explained. Note, however, that we found low head circumferences at diagnosis in patients with a solid tumor (group B, chapter 4).

6.4.5 Prognosis

Several brain tumor patients will need replacement therapy with growth hormone or growth hormone releasing factor,[93-95] because of hypothalamic and/or pituitary dysfunction. After spinal irradiation, sitting height will show less growth than height and armspan, which will result in disproportional catch-up growth. The head growth after cranial irradiation may prove to be impaired after a follow-up of more than 2 years.[92]

A catch-up growth of height can be expected in ALL patients, at completion of therapy[7,26,54,55,75] and we assume this coincides with a catch-up growth of sitting height and armspan (group 7). In patients treated with cranial irradiation (for brain tumors as well as ALL) a premature pubertal development may occur,[96-98] while pubertal growth may be disturbed.[99,100] The ultimate adult height may therefore be below normal. Probably the dose of cranial radiation was too small to cause a growth retardation of the skull. The weight gain in the ALL patients may go on after cessation of treatment and obesity may persist for another 5 years or more.[50,89]

The retarded height and weight growth in the patients with a Wilms' tumor is made good as early as 1 year after diagnosis. The abdominal irradiation dose is presumably not large enough to cause reduced sitting height. The growth of patients of group 6 is hardly affected; no further problems are to be expected for them in the future.

CHAPTER 7

BONE AGE OF CHILDREN WITH ALL DURING AND AFTER TREATMENT

7.1 INTRODUCTION

Children with acute lymphoblastic leukaemia (ALL) at the end of their therapy suffer a height retardation of about 0.5 standard deviation when compared with the beginning of the treatment (chapter 6). This height retardation is made good during the first years after completion of treatment in most patients.

To determine the preserved potential of height growth during treatment for ALL, we investigated bone age (BA) in relation to calendar age (CA) in the children with ALL who were enrolled in our growth study (groups 2-4 and 7).

7.2 NUMBER OF PATIENTS AND BONE AGE ASSESSMENTS

To assess BA one or more X-rays were made of the left hand in 40 ALL patients (25 girls and 15 boys). Basically the X-rays were made annually, but since it was not always possible to do so, the number of X-rays obtained during the study fluctuates somewhat, as can be seen in table 7.1. A total of 164 X-rays were collected. In the table also some patient characteristics are presented. The onset of puberty was set at a breast stage of 2 or up, and at a testicular volume of 4 cc or more. Follow-up did not exceed 5 years. Patients were considered off-study at relapse or at reaching bone maturity (which was defined as adult stage, and

Table 7.1 Characteristics of patients whose bone age was assessed at diagnosis (Dx) or thereafter; for treatment regimes see table 7.2

time from	number		on regime:			age	
Dx (yr)	total	pubertal	1	2	3	mean	range
0	30	3	6	12	12	6.4	1.7-13.9
1	32	5	8	12	12	7.4	2.7-15.0
2	36	6	8	15	13	8.0	3.7-14.2
3	28	10	7	14	7	8.7	4.8-15.1
4	22	8	5	13	4	9.5	5.7-15.5
5	16	4	4	12	0	9.7	6.9-16.2

which concerned 3 girls: 14.8, 14.7, and 16.1 years of age). The patients were treated according to three regimes, all lasting about 2 years. Regime 1 was applied to high risk patients and included cranial irradiation. The regimes 2 and 3 were applied to standard risk patients; regime 2 was applied with and regime 3 without cranial irradiation as CNS treatment (table 7.2). No patient received spinal irradiation or had pre-existing disorders which could cause disturbance of growth or sexual development.

Table 7.2 Differences between 3 treatment regimes used in 40 ALL patients with BA assessments.

regime:	1	2	3
diagnosis	high risk	standard	standard
CNS-treatment			
-i.t. chemotherapy	+ / ++	+	++
-cranial irradiation	18-24 Gy	18-24 Gy	-
-MTX (2 g/m^2)	-	-	+
consolidation	ara-c/ cyclophosphamide	-	-
steroids	prednisone/ dexamethasone	prednisone	dexamethasone

CNS, central nervous system; i.t., intrathecal, MTX, methotrexate.

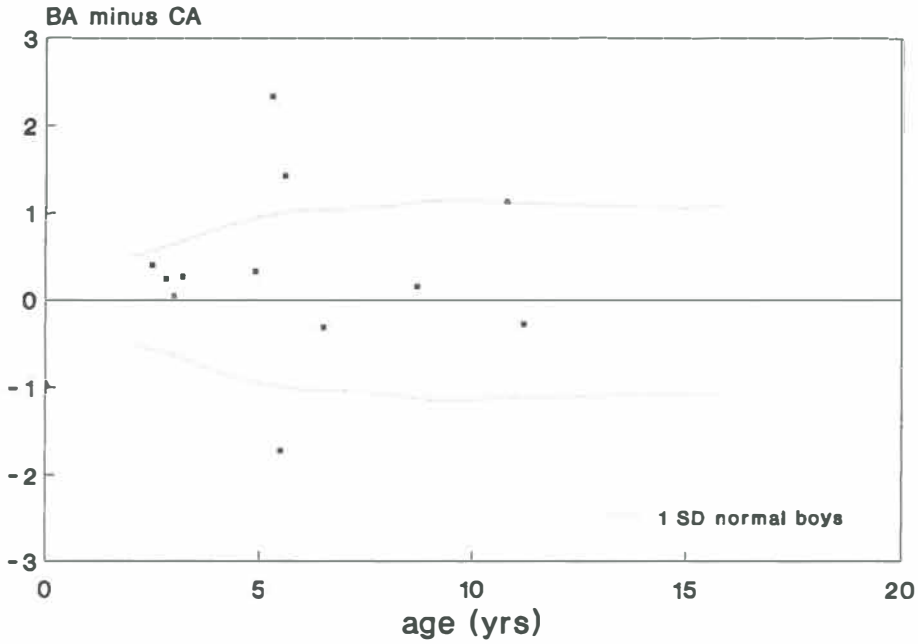
7.3 METHOD, QUALITY AND ANALYSIS OF BONE AGE ASSESSMENTS

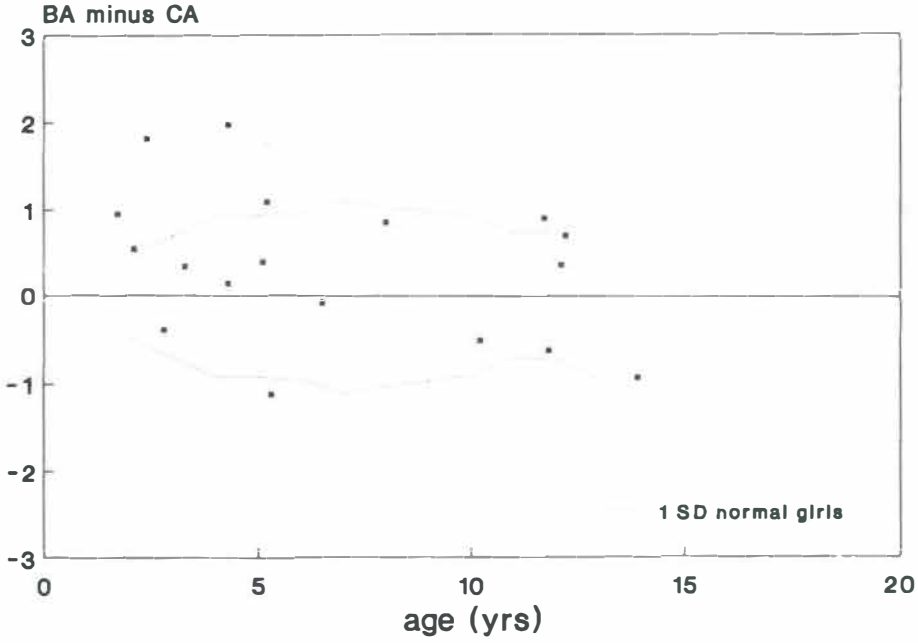
The bone age rating of 20 bones according to the Tanner-Whitehouse II method (TWII-20)[101,102] was done by one person who was trained in the laboratory of Tanner in London. Twelve X-rays (of 6 boys and 6 girls with an age range of 1.9-14.5 years) were rated twice (intra-observer reliability). Of the 240 single bones thus scored, 18 bones (7.5%) were scored differently; in 17 out of the total of 18 cases the difference was only one stage. These results compare favorably with the results reported by Tanner.[102]

The relationship between BA and CA (BA-CA) was calculated by subtraction; the change of (BA-CA) during the study was analysed. These results were compared with the change of z-score (chapter 3) for height in the same patients at the same points in time.

7.4 RESULTS

The difference between BA and CA at diagnosis in 30 patients are presented in figures 7.1a and 7.1b. The reference values +/-1 SD are derived from British





Figures 7.1a and 7.1b Difference between BA and CA at diagnosis in 12 boys (a) and in 18 girls (b) with ALL; longitudinally obtained British reference values are given.[103]

longitudinal standards.[103] Seven patients had a (BA-CA) >1 SD above normal, while 2 had a (BA-CA) >1 SD below normal. The mean BA at diagnosis for the whole study group, was more than .3 year in advance of CA; however, this difference disappeared in the first year of therapy to result into a retardation of >.2 year at the end of therapy; in the 2 years following cessation of therapy BA caught up. No significant differences between patients undergoing different treatment regimes were observed. The development of the mean of (BA-CA) during the follow-up is about the same in the three groups (figure 7.2). This method of analysis, however, is statistically not satisfactory, because only part of the patients has been investigated at two successive times; in other words the groups investigated at the different times differ to some extent in composition (table 7.1).

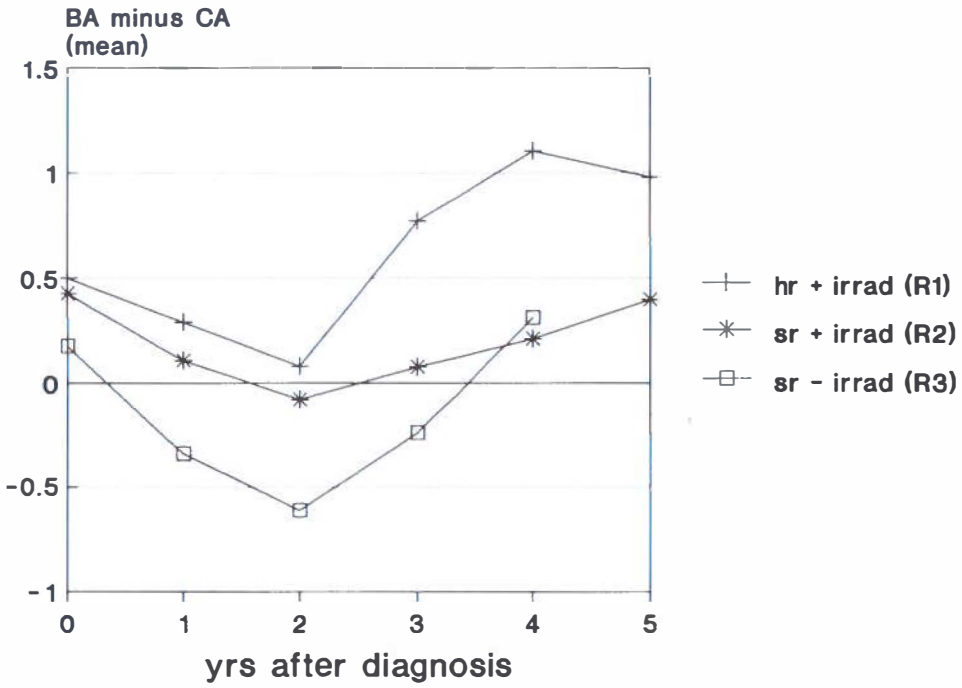


Figure 7.2 Mean difference between BA and CA at diagnosis of ALL and during 5 years of follow-up; the patients are stratified in three groups according to the treatment regime they received: hr, high risk; sr, standard risk; +/- irrad, with or without cranial irradiation (see table 7.2).

The change of (BA-CA) between two BA assessments in the same patient is the most significant characteristic. The results per individual for the period during treatment and/or for the first 2 years after treatment, are presented in figure 7.3. During treatment in 19 out of 27 patients a retardation occurred, while after treatment in 16 out of 20 patients a catch-up occurred. The mean

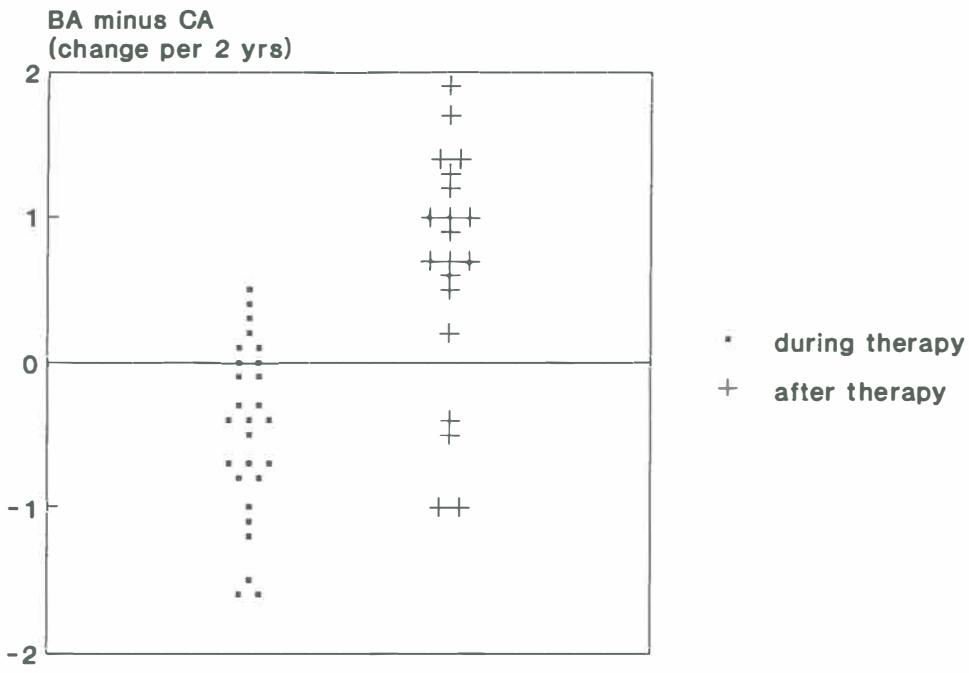


Figure 7.3 Change in difference between BA and CA per individual during 2 years of treatment and during 2 years after completion of treatment.

change of (BA-CA) per year are displayed in table 7.3. The largest decrease of (BA-CA) occurred in the first year of therapy, the main catch-up in the 2 years after completion of therapy. Again no differences could be found between the patients on the three different regimes (figure 7.4).

Table 7.3 Change of BA minus CA and the change of z-score for height, during intervals of 1 yr, starting at diagnosis.

interval		BA-CA		z-score	
(yrs)	n	mean	sd	mean	sd
0-1	30	-.36*	.44	-.36*	.37
1-2	29	-.16	.48	-.21*	.32
2-3	26	.33*	.73	.34*	.35
3-4	21	.40*	.63	.13*	.24
4-5	14	-.06	.36	.03	.23

* significant different from zero (Student's t-test, $p < .05$)

A significant correlation between (BA-CA) and z-score for height was found at all times of BA assessment; the correlation coefficient ranged during the

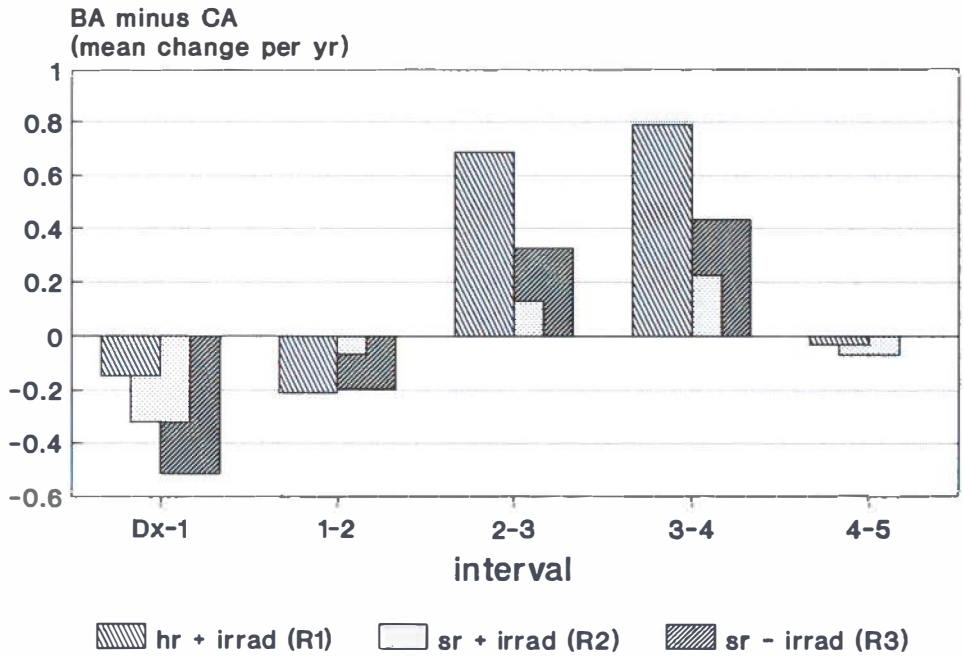


Figure 7.4 Change in difference between BA and CA during intervals of 1 year from diagnosis (Dx) in three treatment groups (for stratification see legend to figure 7.2).

study from .45 to .77. This indicates that height retardation coincides to some extent with BA retardation and vice versa.

The mean change per year of z-score for height is also presented in table 7.3. The mean change of the z-score during the study parallels the mean change of (BA-CA).

BA retardation during the period of therapy was correlated with catch-up during the period thereafter. There was no difference between boys and girls. A statistically insignificant correlation was found between age and catch-up of (BA-CA) after completion of therapy, which indicates that younger patients may have a greater ability to catch up on bone age development than older ones.

7.5 DISCUSSION

In this longitudinal study of bone age development, we found a small positive difference between BA and CA at diagnosis using British standards. Such a positive difference has been reported previously for healthy children[17,104] and is probably not related to ALL. During the period of treatment a BA retardation occurred which was followed by a catch-up after completion of therapy. Mean bone age correlated positively with mean height.

We believe that it is those constituents of the therapy which are administered during the whole of the period of treatment that are responsible for our findings and not the leukaemia or the cranial irradiation, which takes place at the beginning of the treatment period. Two arguments to support this notion are that no difference existed between patients treated with and without cranial irradiation and that a catch-up did not occur before treatment was completed.

The present report is, to our knowledge, the first focussing on bone age development in ALL patients. However, a considerable number of studies concerning growth and/or pubertal development in ALL patients has been published. In previous growth studies both normal[56] and retarded[65] bone age during treatment has been reported; after completion of treatment only normal bone ages are reported.[7,48] In the studies concerning pubertal development early as well as late sexual development have been reported in combination with advanced or retarded bone age. A major cause for early sexual development is thought to be cranial irradiation[97] and for late sexual development gonadal damage (e.g. after testicular irradiation). In our study no patient showed an early sexual development. A number of patients, however, were in puberty (table 7.1); 5 of them showed a retardation of at least one secondary sex characteristic (chapter 8). However, we don't think that gonadal damage is the main cause of our findings of BA retardation, because it occurs not only in (near) pubertal patients but also in the very young.

Bone age retardation has been described in patients with other diseases than ALL, e.g. with enuresis,[105] allergic disease,[106] sickle-cell anaemia,[107] celiac disease,[108] diabetes mellitus,[109] and chronic kidney disease.[110-113] In some of these patients the retardation of height and bone age has been associated with corticosteroid treatment, especially when given continually and in high doses,[86,87,110,111] while alternate day therapy does not affect bone age.[114] The patients in our study also received corticosteroids during the entire period of treatment, but only intermittently (2 weeks of steroid treatment, 5 weeks off, every 7 weeks, for a total of 104 weeks). Therefore, concomitant medication (e.g. methotrexate) may play an additional role.

To conclude, we found a retardation of BA development during treatment for ALL parallel to the decrease in height growth; therefore the growth potential seems unimpaired.

CHAPTER 8

PUBERTAL DEVELOPMENT OF CHILDREN WITH CANCER TREATED JUST BEFORE AND DURING PUBERTY

8.1 INTRODUCTION

The treatment of cancer in children may induce variable defects, e.g. retardation of physical growth (chapter 6) and bone maturation (chapter 7). Moreover, chemotherapy and/or radiotherapy are often associated with a considerable delay in sexual development.[15] In contrast, some authors have mentioned premature sexual development, as a consequence of cranial irradiation during infancy or childhood.[96-98]

We have investigated the appearance of the secondary sex characteristics in the children involved in our growth project, aged 8-16 years at diagnosis.

8.2 PATIENTS

Of the 134 children participating in our growth study, 43 (22 boys and 21 girls) were more than 8 years of age at diagnosis. Thirty patients were studied from diagnosis (project A) and 13 from the cessation of therapy (project B). The median age of the subjects for both sexes at the first measurement was 11.2 years (with a range of 8.3-15.7). The period of observation ranged from 1.0 to 4.0 years with a median of 2.0 years. The median age at the last measurement was 13.6 years (with a range of 10.3-19.7).

Table 8.1 Diagnosis of 43 children with cancer, investigated for sexual development.

Diagnosis	number
acute lymphoblastic leukemia	18
acute non-lymphoblastic leukemia	1
non Hodgkin's lymphoma	3
Hodgkin's disease	2
brain tumors (a.o. medulloblastoma)	7
Ewing's and osteogenic sarcoma	7
other malignant tumors	5

The diagnoses of the patients are given in table 8.1. The patients were treated according to conventional treatment regimes. Of the 18 children with ALL, 15 got cranial irradiation for the treatment of the central nervous system.

8.3 ASSESSMENTS

During the first two years of investigation, the patients were evaluated every three months; thereafter once a year up to a maximum of 4 years after diagnosis. The investigation of the sexual development of the boys included recording the appearance of axillary hair, and the pubic hair stage;[115] in addition the testicular volume was estimated with an orchidometer.[116] In girls the appearance of axillary hair, the stage of pubic hair, the breast development[117] and the onset of menses (menarche) were used as criteria for determining sexual development. In the case of hair loss due to chemotherapy the results were recorded as non-existent. Height and weight were measured in both sexes.

Other parameters that were used were plasma levels of LH, FSH, testosterone, estradiol and dihydroepiandrosteronesulphate (DHEAS). In addition X-rays of the wrist were made annually from the time of diagnosis onward, in order to assess bone age.[118]

8.4 ANALYSIS

Several standards for the development of the secondary sex characteristics are available, e.g. the longitudinally obtained British standards[119] and the more recently obtained cross-sectional Dutch standards.[120] We preferred the British standards, because like our own data, they were obtained longitudinally. A comparison of the Dutch standards and the British shows that the various stages of sexual development are reached at an earlier age in the Dutch population than in the British population. Thus we regarded patients with a development of under the tenth percentile ($<P_{10}$) as retarded, according to the British standards. No normal values for the appearance of axillary hair could be found; therefore we arbitrarily decided to regard an appearance after the age of 14.5 years as late in both sexes.

The reference values for the levels of gonadotropic hormones and sex steroid hormones were also obtained from the literature.[120] The Oosterwolde study was again used as a reference for height and weight.[11]

8.5 RESULTS

Of the 43 children, 10 (5 girls) remained prepubertal during the entire period of study for all the secondary sex characteristics; 21 (11 girls) entered puberty for at least one sex characteristic; 12 (5 girls) had already at the beginning of the study entered puberty for all the characteristics (table 8.2). Of the

Table 8.2 Numbers of patients who remained prepubertal or entered puberty during the study and of those who were already pubertal at the start of follow-up. The figures are given for each secondary sex characteristic. The number of patients who were delayed ($<P_{10}$) are given between brackets. See also § 8.5.

sex characteristic	stayed prepubertal		entered puberty		already in puberty		total	
boys								
PH	8	(1)	8	(1)	6	(2)	22	(4)
TV	6	(1)	9	(2)	7	(-)	22	(3)
total boys	5	(1)	10	(2)	7	(2)	22	(5)
girls								
PH	5	(1)	11	(2)	5	(3)	21	(6)
B	5	(1)	11	(3)	5	(1)	21	(5)
M	11	(1)	8	(2)	2	(-)	21	(3)
total girls	5	(1)	11	(3)	5	(2)*	21	(6)
girls and boys total	10	(2)	21	(5)	12	(4)	43	(11)

PH pubic hair development; TV, testis volume; B, breast development; M, onset of menstruation.
* 1 patient (no 8, table 8.3) was in puberty for PH and prepubertal for B and M; she was included in the total of the second column.

10 patients who remained prepubertal, 2 should have entered puberty at the end of follow-up; of the 21 who entered puberty during the study, 5 were late in doing so; of the 12 who were already in puberty, 4 showed an interrupted sexual development.

Figures 8.1-8.5 show of all patients the data concerning the development of pubic hair, breast development, the onset of menstruation, and testicular growth. Additional clinical characteristics of the 11 retarded patients are given in tables 8.3a and 8.3b; the patient numbers in these tables correspond with the numbers in the figures. Two patients (nos. 5 and 8) had a poor nutritional status as defined by a low weight for height. In all patients the bone age was equal to or less than calendar age. In 5 out of 11 patients (nos. 2, 5, 7, 8 and 9) the appearance of axillary hair was late (>14.5 years of age).

With regard to the hormone estimations, the levels of FSH and LH of 2 patients (nos. 3 and 4) were above normal; the levels of FSH, LH as well as those of estradiol and DHEAS in one patient (no. 1) were below normal. Moreover, we found low levels of DHEAS in relation to age in four patients (nos. 5, and 7-9); in all children, however, the levels of DHEAS parallelled the sexual development, that of pubic hair in particular.

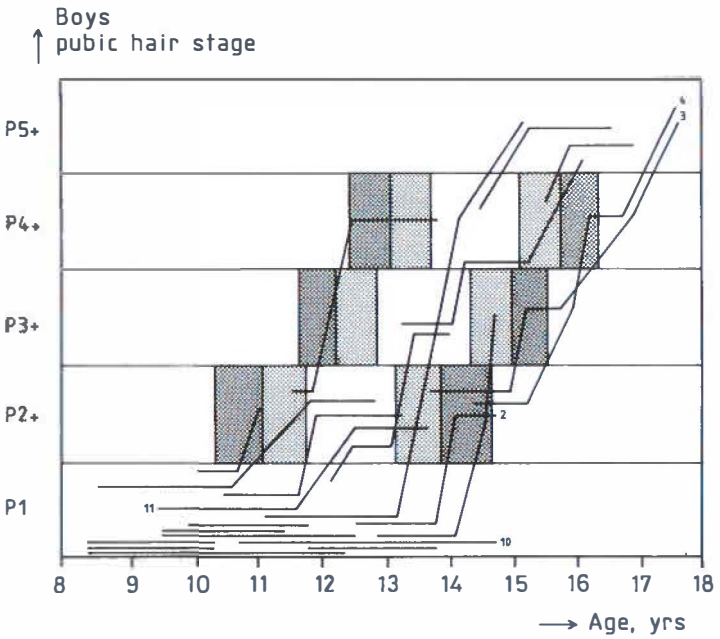


Figure 8.1 The stage of pubic hair of 22 boys treated for cancer. Numbers correspond with those in table 8.3. Shaded areas represent the normal values in percentiles at which age a particular stage is to be reached; from left to right: $P_{97\cdot90}$, $P_{90\cdot75}$, $P_{75\cdot25}$, $P_{25\cdot10}$, $P_{10\cdot3}$. Normal values for the adult stages are not given since these continue indefinitely.[119]

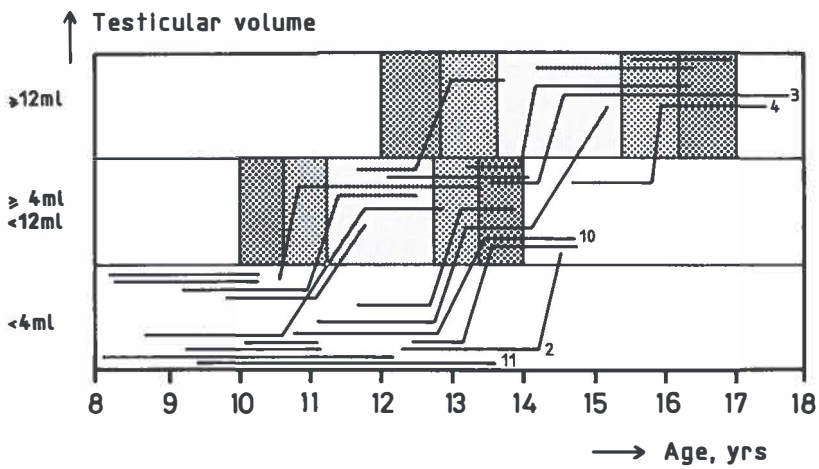


Figure 8.2 Testicular volume of 22 boys treated for cancer. Also see legend to figure 8.1.

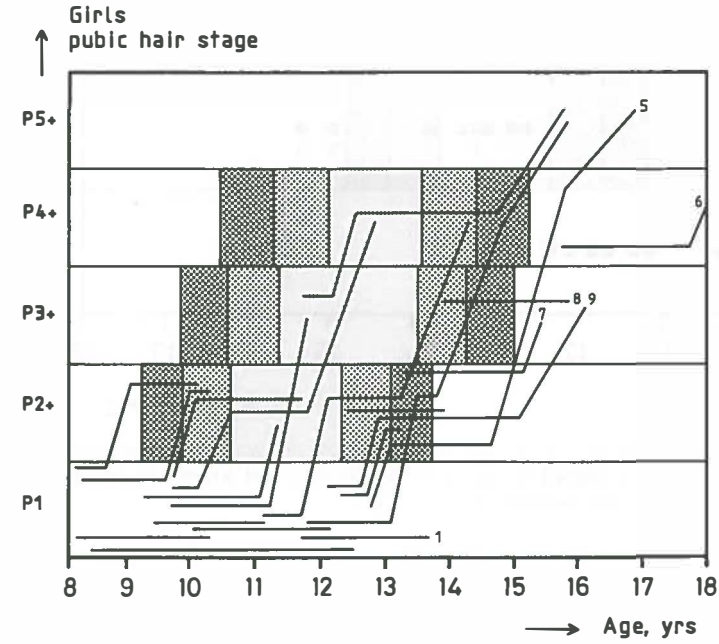


Figure 8.3 The stage of pubic hair of 21 girls treated for cancer. Also see legend to figure 8.1.

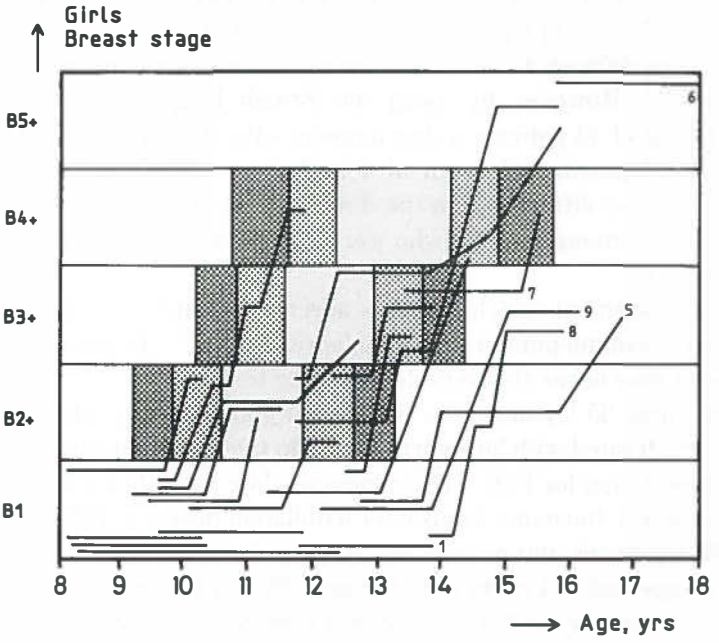


Figure 8.4 The stage of breast development of 21 girls treated for cancer. Also see legend to figure 8.1.

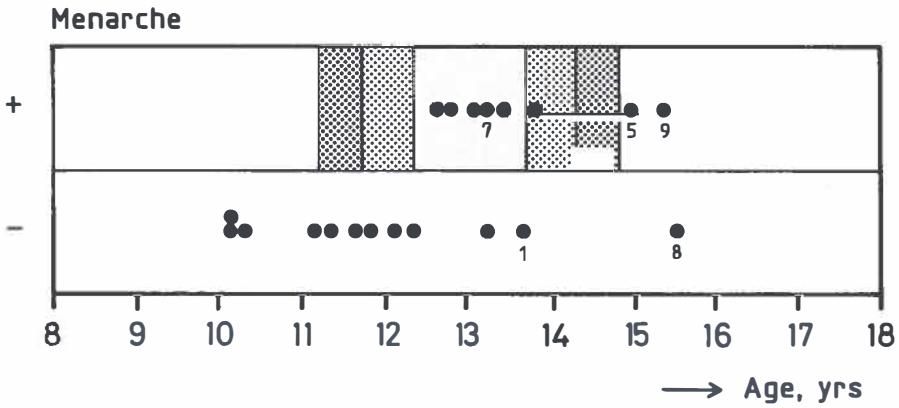


Figure 8.5 Age at onset of menses (+) or age at last follow-up when no menarche has occurred (-) in 20 girls treated for cancer; menstruation had already started before diagnosis in one girl. Also see legend to figure 8.1.

8.6 DISCUSSION

In this chapter we present the results of a study of pubertal development in children with cancer; all children were more than 8 years old at diagnosis. Existing standards for the development of secondary sex characteristics show a wide range of the appearance of these characteristics in the normal population, which makes it very difficult to come to definite conclusions concerning delayed development.[115,117] However, by using the British longitudinal standards, we found in 11 out of 43 patients a development $<P_{10}$; 24 out of 43 children had a normal development and 8 out of 43, who are still prepubertal, remain at risk (table 8.2). No differences in the development of secondary sex characteristics were found among patients who were prepubertal or pubertal at the beginning of the study.

A normal sexual development which includes adrenarche and gonadarche requires an intact hypothalamo-pituitary-gonadal/adrenal axis.[121] Impairment due to cancer treatment may occur at several levels along this axis.[15]

Irradiation of more than 35 Gy increases the risk of gonadotropic deficiency.[122,123] Patient no. 1 was treated with 50 Gy irradiation to the optic chiasma and requires hormonal substitution for FSH/LH deficiency, while patients no. 2 and 4 had adequate gonadotropic hormone levels after irradiation doses of 35 Gy.

The elevated FSH/LH levels and normal testosterone levels in patients no. 3 and 4, indicate a compensated Leydig cell damage. This is probably due to the chemotherapy[15,124,125] and/or scatter irradiation to the testes[126] (patient no. 4). From the remaining 8 patients (nos. 2 and 5-11) none had elevated FSH/LH levels. This is remarkable because 7 out of 8 had already entered puberty for at

Table 8.3a Clinical data of 11 patients with a sexual development less than P_{10}.

pt	sex	age (yrs)	diagnosis	radiotherapy dose (Gy)/site	chemotherapy[a] (alphabetically)
1	F	11.5	optic glioma	50/local	-
2	M	12.5	medulloblastoma	35/craniospinal 30/local	CCNU VCR[148]
3	M	13.8	Ewing's sarcoma	-	ADR BCD MTX VCR[149]
4	M	14.7	medulloblastoma	35/craniospinal 20/local	MTX procarbazine[150]
5	F[c]	12.7	Hodgkin's disease	40/mediastinal 30/abdominal	ABVD MOPP[151]
6	F	15.7	osteosarcoma	-	ADR BCD HD-MTX VCR[152]
7	F	11.5	ALL-SR[b]	24/cranial	ASP DNR 6MP MTX PDN VCR[153]
8	F	13.9	ALL-SR	24/cranial	ASP DNR 6MP MTX PDN VCR[153]
9	F	12.1	ALL-SR	-	ASP DXM HD-MTX 6MP MTX VCR
10	M	10.9	ALL-SR	-	ASP DXM HD-MTX 6MP MTX VCR
11	M	9.6	ALL-SR	24/cranial	ASP DNR 6MP MTX PDN VCR[153]

[a] ABVD: ADR, BLEO, vinblastine, dacarbazine; ADR, adriamycin; ASP, l-asparaginase; BCD, bleomycin, cyclophosphamide and actinomycin D; DXM, dexamethasone; HD-MTX, high dose methotrexate; MOPP: mitoxin, VCR, PDN, procarbazine; 6MP, 6-mercaptopurine; PDN, prednisone; VCR, vincristine.
[b] ALL-SR, acute lymphoblastic leukemia standard risk.
[c] oophoropexia was performed during staging laparotomy.

Table 8.3b Weight for height, delay in bone age and development of secondary sex characteristics in 11 patients with a sexual development less than P_{10}.

pt	W/H (%)	BA-CA (yrs)	PH (%)	B (%)	TV (%)	M (%)	Ax (yrs)
1	25	-1.5	<3	<3		<25	>13.5
2	<10	-2.5	10		<3		>14.5
3	10	0	3-10		50		D
4	10	-1.0	3-10		10-25		D
5	<<10	-2.5	3-10	<3		<3	15.8
6	10	0	<3	D		D	D
7	10	-1.5	<3	3-10		25	14.9
8	<<10	-1.5	<3	<3		<3	15.2
9	10	-1.0	<3	<3		<3	>15.2
10	10	-1.0	<3		3-25		>13.8
11	10	-0.5	50		3-10		>13.6

W/H weight for height; BA-CA, maximum bone age delay with respect to calendar age; PH, pubic hair development; B, breast development; TV, growth of testis volume; M, onset of menstruation; Ax, appearance axillary hair; age.
% percentiles.
D mature stage at diagnosis.

least one characteristic. 2 out of 8 in particular (nos. 2 and 5) had received potentially gonadotoxic drugs, in addition to scatter irradiation onto their gonads.[127,128] In these patients a transient gonadal dysfunction, existing before they entered puberty may have been responsible for the clinically observed

delay in pubertal development; such a dysfunction cannot always be found by estimating the basal gonadotropin levels and can therefore be easily underestimated.[129-131] Biochemical and clinical studies,[130,132-134] and in particular morphological studies,[135-138] have shown that the prepubertal gonad is sensitive to cancer treatment, though maybe less than the postpubertal gonad.[129,132] Our observations are consistent with these findings.

Adrenal hormones are decisive for the timely appearance of axillary hair and pubarche. A deficient adrenal function therefore may delay the development of pubic and axillary hair. Where chemotherapy induced a general loss of hair, we regarded the relevant data concerning the development of pubic hair as nonexistent. However, it is conceivable that when the hair started to grow again after the cessation of chemotherapy, we wrongly recorded a pubic hair stage below normal. This might have happened especially in patients no. 3, 4 and 6, in whom pubic hair development was more delayed than the other sex characteristics (breast development/testicular volume). However, patients 1, 5 and 7-10 had a delay in pubic hair similar to the delay in other secondary sex characteristics. The late increase in the levels of DHEAS parallelled in all the 11 patients the delay in sexual development. Corticosteroid treatment in the patients with ALL and Hodgkin's disease can also have resulted in low DHEAS levels, although the intermittent administration of these drugs makes this less likely.

In addition to the adverse effect of cancer treatment, stress and poor nutritional status, which are commonly seen in cancer patients, can result in a delay of sexual development. Physical and mental stress are for example thought to suppress LH and FSH release.[132] Moreover, in the present study 2 patients (nos. 5 and 8) show a severe retardation of weight growth (weight for height $<<P_{10}$). It is difficult to differentiate between late sexual development due to the above mentioned general factors and constitutional delay; it is possible that in individual patients both phenomena have contributed to a delay in sexual development.

In our study 9 out of 11 patients had a retarded bone age (table 8.3b) parallel to the delay of the development of secondary sex characteristics. Although it is known that in healthy children a large variation in bone age exists, our data suggest a relationship between the different maturation parameters. Marshall, however, reported that the maturation of the skeleton in prepubertal children is independent of other maturational processes.[139]

Premature instead of late sexual development in children has recently been reported.[96-98] The patients mentioned in these reports had all received cranial irradiation for ALL or a malignant solid tumor. The authors suggest that the irradiation causes a premature activation of the hypothalamo-pituitary-gonadal axis, resulting in a precocious or early sexual development. The patients were usually diagnosed and treated at a younger age than the patients selected for our study (>8 years at diagnosis). We did not find any early sexual development

in our 43 patients. This is consistent with Leiper et al., who have found a relation between beginning the treatment of a patient at an early age and early menarche.[97]

In conclusion we can say that we found a delayed or interrupted sexual development in 11 out of 43 children with cancer. All 11 patients were pubertal or just before puberty at diagnosis. No differences were found between patients who were pubertal or prepubertal at the beginning of the study. In three cases hypothalamo-pituitary damage or gonadal damage could be found. In the other 8 patients no evidence for a single cause was found, but transient prepubertal gonadal damage, poor nutritional status, intermittent corticosteroid administration, or stress may have been involved. Our findings emphasize the need for a proper counseling of patients and parents in order to prevent or reduce psychosocial problems at a later age.

CHAPTER 9

CONCLUSIONS AND PERSPECTIVES

9.1 INTRODUCTION

At the time when we started our study (1982), growth retardation during treatment and catch-up growth after completion of therapy had already been reported.[3-10] However, the identification of treatment regimes with a major adverse impact on growth was not at all complete, particularly because longitudinal prospective studies were rare. It is for this reason that we decided to launch our study, including a follow-up period of 2 years. Patients were stratified according to an estimated growth retardation risk and the probability of catch-up after completion of chemotherapy. The dose of cranial and spinal irradiation, corticosteroid medication and nutritional status proved to be important factors in determining the growth-retardation risk. The cytostatic therapy seemed a less important factor. Using the data provided in chapters 4 and 6, 7 and 8, the following section will illustrate these findings in greater detail.

9.2 CONCLUSIONS

9.2.1 Brain tumor patients

In brain tumor patients, who had usually been treated with high doses of cranial irradiation, we found a progressive height retardation during the 2 years of the study, as did other researchers.[9,10,44-46,70,76-78] This height impairment, with a mean of .72 standard deviation unit, comes on top of the height retardation already existing at diagnosis in some of these patients.

Armspan and sitting height were affected in the same way as height was. Despite the spinal irradiation, which most of these children received, no disturbed relationship could be established between height and sitting height. The period of study is presumably too short to yield such results.[70,72] It is for the same reason, probably, that no retardation of the head circumference could be detected, although this may also have been caused by the fact that most head growth occurs during early childhood.

Children with a brain tumor who are more than 8 years old at diagnosis are at considerable risk for a delay in pubertal development, even when the tumor is located outside the hypothalamo-pituitary region. Apart from cranial irradia-

tion,[122,123] both chemotherapy[126] and scatter irradiation of the gonads[127] may be responsible for this. On the other hand, premature pubertal development in these children has been reported.[96,98]

9.2.2 ALL patients

No abnormal results were found in ALL patients at diagnosis, except for a long armspan. Moreover, only two individuals were very tall at that time. Thus, no clear evidence was found to associate tall stature or rapid growth with ALL.[23-26]

The height retardation found in ALL patients during treatment was less than in brain tumor patients (.64 to .36 standard deviation unit). Most height impairment occurred in the first year of therapy.[3,22,26,50,54,55] A catch-up growth was found after cessation of treatment.[7,26,54,55,75] No difference was recorded between patients with and without cranial irradiation as CNS treatment.[55,64] Therefore we conclude that the chemotherapy including corticosteroids, is a major cause of the growth retardation in these patients. Cranial irradiation, however, may play a role here as well.[4-6,22,48,52,56-61]

The bone age was also investigated in these patients. We found a retardation and catch-up of bone age development parallel to the changes of height growth, without any difference between patients treated with and without cranial irradiation. This supports our view that the medication has a major influence on height growth. A delay of the pubertal development is not a likely explanation for our findings, though some children had a late pubertal development, as well.

The catch-up of height and bone age promises an unimpaired ultimate height. However, the occurrence of a disturbed pubertal growth[99,100] and/or a premature pubertal development after cranial irradiation[97] may result in an adult height below normal.

The other linear variables were retarded in the same way height was. Armspan, however, was significantly more sensitive to growth retardation than sitting height. No significant correlation with age could be found.

The increase of weight in relation to height (parallel with upper-arm circumference) was considerably above normal in most ALL patients.[50,67,89] A very low weight for height, however, was found in one of the patients with a retarded pubertal development, which may in part explain this late pubertal development. We found that the abnormal weight gain tends to go on after completion of therapy, probably resulting in obesity.[50,89]

9.2.3 Wilms' tumor patients

At diagnosis Wilms' tumor patients had a weight for height below normal, which was probably caused by the disease; subsequently, weight became normal within 6 months after diagnosis. These changes of nutritional status are responsible for the height retardation observed during the first 6 months after

diagnosis and the subsequent catch-up during the next 6 months. This catch-up was apparently not impeded by the chemotherapy that was given.

No reduced sitting height could be observed in these patients, despite abdominal radiotherapy. This may be due to the radiation dose being too low, the radiation field being too small and/or the follow-up too short for establishing a disturbed relationship between height and sitting height.[71]

9.2.4 Patients treated with high doses of cyclophosphamide and/or methotrexate

These patients, with various diseases, showed a poor nutritional status at diagnosis.[40] Weight for height was back to normal within 2 years. No retardation of the linear growth variables was found. The relative high age of these patients at diagnosis might account for this. A catch-up for height was observed, however, in a different group of patients treated similarly. This contrast is probably caused by differences in the composition of the patient groups.

In two of these patients a late or interrupted pubertal development was noted. The cytostatic drugs, which they received are known to be able to cause gonadal damage.[15,124,125]

9.3 PERSPECTIVES

While carrying out this research, we encountered several difficulties. One problem was that relatively large numbers of participants are necessary, resulting in a long accrual period. Treatment regimes may have changed before a sufficient number of patients have been selected for the study. This problem can be solved by cooperating closely with other researchers treating patients in a similar way. It is likely, however, that in such a joint study more anthropometrists are involved, which will make it more difficult to reach an acceptable level of precision in the measurements.

A characteristic of growth studies in general is, of course, that it takes some time to detect growth changes in an individual patient. Therefore it was impossible for us to make definite statements about the impact that specific drugs, chemotherapy courses, radiotherapy and/or supportive care have on growth. A method to measure changes of growth in a relatively short period of time (a few weeks) has recently been developed. It is based on the measurement of the length of the lower leg and is called knemometry.[140] With this method it may be possible to detect growth changes, e.g. as a consequence of a particular chemotherapy course, though in our study the cytostatic treatment did not seem to have a major adverse impact on growth. The usefulness of knemometry for clinical practice and/or research has not, however, been established conclusively.[141,142]

In addition, it is important to investigate the mechanisms by which cancer treatment causes changes in growth. Thorough hormonal studies are necessary

for that. Growth hormone has been investigated particularly in patients with brain tumors and ALL, but no longitudinal studies have been performed. Part of the explanation is probably to be found in the fact that the procedures involved in growth hormone studies, such as frequent blood sampling and (sometimes) hospitalization, are a burden to the patient. This problem can now be overcome, since growth hormone can be measured in urine samples.[143-145] Short term changes of growth hormone release, as a result of a specific part of cancer treatment can thus easily be analysed. In addition to growth hormone, other hormones such as somatomedin C and its inhibitors,[146,147] should be studied as well.

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APPENDIX

THE METHODS OF MEASUREMENT

The measurements were performed according to the guidelines of Cameron.

1. Stature and sitting height
The Harpenden stadiometer and the Harpenden sitting height table were used. For stature the heels were placed in such a way that either the ankles or the knees were together. For both measurements the child's head was held in such a way that the orbits were in the same horizontal plane as the external auditory meati. Both measurements were taken while a gentle upward pressure was exerted on the mastoid process and the child stretched as much as possible by taking a deep breath. A weight of 500 grams was placed on the headboard.

2. Armspan
A measuring rod was used to measure armspan. This rod was fixed in the horizontal plane but could slide in the vertical plane. The arms were fully extended and the distance between the tips of the stretched middle fingers was measured.

3. Length of arm, hand, tibia and foot
To determine the length of the arm, hand, tibia and foot the Harpenden anthropometer was used. First the distance between the lateral border of the acromion and the head of the radius was measured with the arm hanging down. In addition the distance between the head of the radius and the end of the radius was measured with the arm hanging loosely by the side of the child. The length of the hand was determined by measuring the distance between the tip of the third finger to the end of the radius, with the hand and forearm flattened out on a table. The length of the tibia was established by measuring the distance between the proximal-medial border of the tibia and the distal border of the medial malleolus. The length of the foot, finally, was determined by measuring the distance between the most posterior part of the heel and the first toe, with the child in a standing position.

4. Biacromial and biiliacal diameter
Again the Harpenden anthropometer was used. While the child relaxed its shoulders, the distance between the most lateral borders of the acromial pro-

cesses was measured to determine the biacromial diameter. The distance between the widest points of the iliac crest was measured to determine the biiliacal diameter.

5. Weight
An electronic scale with digital reading was used.

6. Circumferences
A fiberglass reinforced tape measurer of plastic was used. The head circumference was measured placing the tape over the most protruding point of the occiput and the most anterior protuberance of the forehead. The upper-thigh circumference was measured with the child in a standing position and with the tape placed horizontally at the level of the gluteal fold. The calf circumference was measured at its maximum point with the child sitting on a table, its feet free from the ground and the calves relaxed. The upper-arm circumference was measured midway between the acromion and olecranon with the arm relaxed and hanging loosely by the side of the child.

SUMMARY

GROWTH OF CHILDREN WITH CANCER

Between 1982 and 1988 the divisions of oncology and endocrinology of the Department of Pediatrics conducted a prospective and longitudinal investigation into the growth of children with cancer. At regular intervals of 3 months and during a period of 2 years, several anthropometric measurements (14 in all) were performed and the development of a number of secondary sex characteristics was studied. In addition an X-ray of the left hand was made each year. 104 patients entered the study at diagnosis and a further 26 at completion of therapy.

The two reliability studies that were conducted revealed some differences in precision among the observers, as well as a number of systematic errors concerning some anthropometric variables. However, the results of the reliability studies are in line with the results of similar studies. Admittently, further analysis was restricted, to the measurement results of height, weight (for height), upper-arm circumference, armspan, sitting height and head circumference.

The anthropometric data were transformed into z-scores with a contemporary, cross-sectional study (Oosterwolde) as reference; this enabled us to compare different groups of patients of varying age and sex. A growth-curve model for the series of 9 z-scores obtained during 2 years was proposed, based on the parabola of closest fit. This enabled us to establish changes of growth rate in patient groups differing from each other, or from a group of healthy children. Data concerning these healthy children were derived from the Nijmegen mixed-longitudinal growth study. The children from Oosterwolde proved to be, on average, larger than the children from Nijmegen. The application of the proposed model to the Nijmegen data, confirmed the theory (except in the case of sitting height). Our method to establish growth-rate deviations, therefore, appeared to be valid.

Analysis of the measurement results concerning 96 patients at diagnosis, showed a normal height, sitting height and midparent height. The analysis did reveal a long armspan (in the case of leukaemia patients and of patients with a solid tumor), but this was not considered to be conclusive evidence for the suggestion that rapid growth and tall stature are associated with cancer. Also, the nutritional status of patients with a solid tumor at diagnosis proved to be less than optimal.

Of the 130 patients who entered the study, 79 could be evaluated for analysis of the longitudinal data. They were stratified into 8 groups on the basis of the

presumed growth-retardation risk of the treatment they got (groups 1-6) and of the possibility of catch-up growth after completion of treatment (groups 7 and 8). Patients treated with high doses of cranial irradiation (for brain tumors) showed a persistent growth retardation for height, sitting height and armspan. Less retardation for these variables was found in patients treated for acute lymphoblastic leukaemia (ALL). Armspan appeared to be more affected by growth retardation than sitting height. No differences were found between ALL patients that did receive cranial irradiation and those that did not. Therefore we think that the retardation is caused by the medication (cytostatics and corticosteroids) and not by the cranial irradiation. A catch-up growth for e.g. height could be established after completion of therapy. Weight for height growth was excessive during treatment, particularly in patients who received dexamethasone. The height growth of patients with a Wilms' tumor was only retarded in the 6 months after diagnosis, which was probably caused by a poor nutritional status at diagnosis. Patients treated with high doses of cyclophosphamide and/or methotrexate showed no retardation at all. No abnormal relationship between height and sitting height could be established in patients who received irradiation of the spine (brain tumor patients and Wilms' tumor patients). Possibly the follow-up period of 2 years is too short.

In 40 children with ALL, followed up to 5 years after diagnosis, 163 bone age (BA) assessments were performed according to the Tanner-Whitehouse II method based on 20 bones. The development of BA in relation to calendar age was retarded during treatment and made good completely after cessation of therapy. The BA retardation thus parallels the height retardation in these children, preserving the potential of unimpaired height growth. No differences were found between patients that did receive cranial irradiation and those that did not. Again we think the cytostatics and/or corticosteroids play a causative role.

The pubertal development was investigated in 43 children who were older than 8 years at diagnosis. Eleven of these children showed a late or interrupted pubertal development. No premature onset of puberty was noted.

The results of the present study indicate that it could be worthwhile for future researchers to study growth changes during very short periods of time using knemometry. This would enable them to differentiate more accurately the potentially adverse effect on growth of the separate components of the treatment given. In order to reveal the pathogenesis of the growth retardation, hormone levels will have to be studied. The possibility of measuring growth hormone in urine samples gives the opportunity to investigate growth hormone release at various times during the treatment of an individual patient.

SAMENVATTING

GROEI VAN KINDEREN MET KANKER

§1. Inleiding.
De overlevingskans voor kinderen met kanker was 30 jaar geleden zeer klein. Toen was men vooral bezig met het vergroten van deze overlevingskans. Tegenwoordig overleeft ongeveer 50% van de kinderen met kanker en wordt er meer aandacht geschonken aan mogelijke nadelige gevolgen van de aandoening en de behandeling. In dit verband is in het Academisch Ziekenhuis Groningen vanaf 1982 onderzoek gedaan naar de groei van kinderen met kanker. We verwachtten in het algemeen dat de lengtegroei tijdens behandeling zou verminderen en dat na het beëindigen van de behandeling een inhaalgroei zou optreden. Hoofddoel van het onderzoek was om na te gaan voor welke behandelingsmethoden en groepen patiënten deze verwachting klopte.

Er deden 104 kinderen aan het onderzoek mee vanaf diagnose, en 26 na voltooiing van de behandeling. Alle kinderen werden ten minste 2 jaar gevolgd zolang het goed ging met hun ziekte. De kinderen werden iedere 3 maanden onderzocht. Tijdens het onderzoek werden lengte en gewicht, schedelomtrek, spanwijdte (afstand tussen de toppen van beide middelvingers wanneer de armen opzij gestrekt zijn), zithoogte (lengte tijdens zitten vanaf zitvlak), omtrek van de bovenarm en vele andere lichaamsmaten gemeten. Ook werd er gekeken naar de puberteitsontwikkeling en werd er ieder jaar een röntgenfoto van de linker hand gemaakt, ter bepaling van de skeletleeftijd.

In de eerste paragrafen wordt iets verteld over de nauwkeurigheid van de metingen (§2), de referentiepopulatie (§3), de bevindingen bij diagnose (§4) en de methode die we gebruikt hebben om een serie metingen van eenzelfde patiënt te analyseren (§5). In §6-§8 vermelden we vervolgens de bevindingen van ons onderzoek. Tot slot geven we nog enkele aanwijzingen voor toekomstig onderzoek (§9).

§2. Nauwkeurigheid.
De metingen werden verricht door twee meetassistentes; tijdens het onderzoek is er 3 keer een vervanging van een van hen geweest. Meer dan 80% van de lengtemetingen zijn volgens plan uitgevoerd.

We zijn nagegaan hoe nauwkeurig de meetassistentes maten. Er is gekeken of er verschillen waren wanneer dezelfde assistente twee keer achter elkaar eenzelfde scholier mat. Ook werd er onderzocht of er verschillen bestonden tussen

twee assistentes die achtereenvolgens eenzelfde patiënt maten. Er bleek inderdaad een verschil in nauwkeurigheid te bestaan tussen de assistentes. Ook bleek dat de ene assistente systematisch bepaalde lichaamsmaten (bijvoorbeeld de lengte van de bovenarm) anders mat dan de andere assistente. Uit praktisch oogpunt zijn deze resultaten echter niet erg storend, zeker niet voor zo ver het de eerder genoemde, en waarschijnlijk belangrijkste, lichaamsmaten betreft. De meetnauwkeurigheid van onze assistentes kwam goed overeen met die van anderen in soortgelijke studies.

§3. Referentiepopulatie.
Een extra probleem bij het vergelijken van groepen patiënten was het verschil in leeftijd en geslacht. Een groep met veel meisjes van 12 jaar, kan bijvoorbeeld niet goed worden vergeleken met een groep met veel jongens van 3 jaar. Om toch vergelijking tussen de groepen mogelijk te maken, zijn alle meetgegevens omgezet in een zogenaamde z-score. Deze score, voor bijvoorbeeld lengte, wordt bepaald door de lengte van een patiënt, het gemiddelde van de lengte van gezonde leeftijdsgenoten van hetzelfde geslacht en de spreiding rond dat gemiddelde (standaard deviatie). De z-score is nul als de patiënt even lang is als het gemiddelde, kleiner dan nul als de patiënt kleiner is dan gemiddeld en groter dan nul als de patiënt groter is dan gemiddeld. Wanneer, bijvoorbeeld, de gemiddelde lengte van gezonde jongens van 7,5 jaar 129,3 cm is met een standaard deviatie van 5,5 cm, dan is de z-score van een jongen van 7,5 jaar met een lengte van 134,8 cm, precies 1,0. Bij gezonde kinderen ligt de z-score meestal (in 95% van de gevallen) tussen +2 en -2.

Informatie omtrent de gezonde leeftijdsgenoten (referentiepopulatie) werd verkregen uit een studie die in Oosterwolde is uitgevoerd. In deze studie zijn dezelfde metingen verricht als in ons onderzoek.

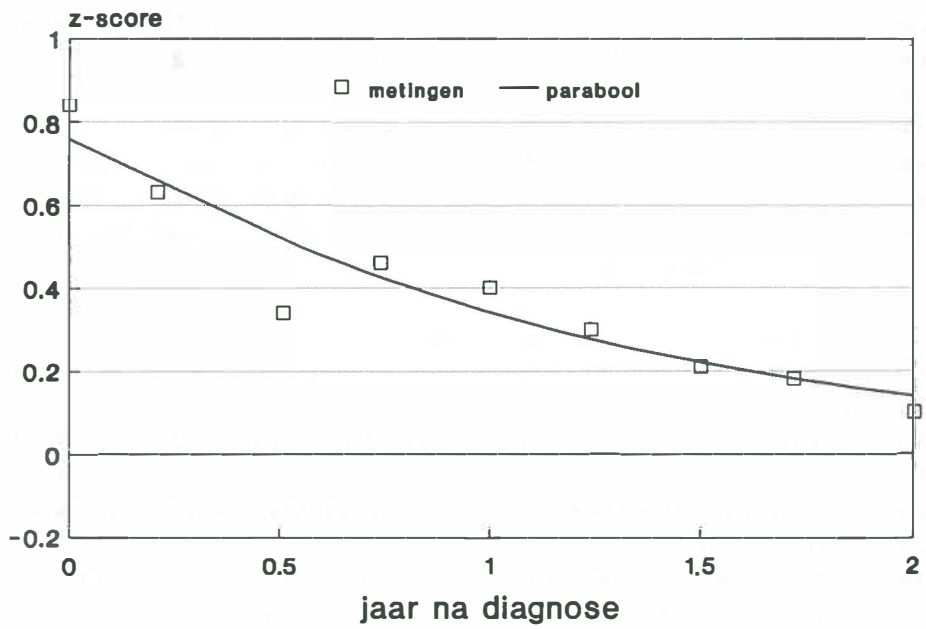
Alvorens deze referentiepopulatie te gebruiken, hebben we de bevindingen van deze Oosterwolde studie vergeleken met de bevindingen van een andere studie van gezonde kinderen, uitgevoerd in Nijmegen. De gemiddelde lichaamsmaten van de kinderen in Nijmegen waren over het algemeen kleiner dan die van de kinderen in Oosterwolde. Een gedeeltelijke verklaring voor deze bevinding is, dat de kinderen in het noorden van Nederland groter zijn dan in het zuiden. Een ander deel van de verklaring is dat de studie in Nijmegen 10 jaar eerder is uitgevoerd dan die in Oosterwolde en dat de kinderen in die tijd langer zijn geworden. Omdat in Oosterwolde veel jongens en meisjes van verschillende leeftijden eenmalig zijn gemeten, concluderen we dat de Oosterwolde studie een bruikbare referentiepopulatie is voor de analyse van eenmalige metingen (zoals bij diagnose, §4).

§4. Bevindingen bij diagnose.
De meetresultaten bij diagnose van 96 patiënten konden worden geanalyseerd volgens de methode van §3. Deze resultaten dienden enerzijds als uitgangssituatie, anderzijds is op grond van ander onderzoek verondersteld dat patiënten met jeugdkanker, langer zijn en/of minder wegen dan gezonde kinderen. Voor deze analyse werden groepen gevormd met leukemiepatiënten, patiënten met een hersentumor en patiënten met een solide tumor (gezwel uitgaande van o.a. spier, bot, nier, bijnier of lever).

We vonden geen verschillen in lengte en zithoogte tussen de patiëntengroepen. Wel was de spanwijdte in de groep patiënten met leukemie of een solide tumor groter dan van patiënten met een hersentumor. De veronderstelling dat een grote lengte of snelle groei iets te maken heeft met jeugdkanker, wordt door onze resultaten dus niet bevestigd.

Verder bleek bij diagnose, op grond van gewicht en omtrek van de bovenarm, dat de voedingstoestand van patiënten met een solide tumor slechter is dan die van patiënten met leukemie.

§5. Methoden voor analyse van een serie metingen.
Het hoofddoel van ons onderzoek was niet zozeer vast te stellen hoe groot een patiënt is, maar veeleer de verandering van die grootte. Gezonde kinderen groeien volgens een bepaald patroon en de vraag was in hoeverre kankerpatiënten afwijken van dat patroon.



Figuur Analyse van de lengtegroei van een patiënt met leukemie.

De patiënten zijn gedurende 2 jaar, iedere 3 maanden gemeten; we hebben dus 9 metingen per patiënt. Deze metingen zijn omgezet in z-scores (§3). We waren, zoals gezegd, vooral geïnteresseerd in het verloop van deze 9 z-scores. Bij gezonde kinderen blijft gemiddeld de z-score gelijk. Wanneer bij een patiënt de z-score echter afneemt dan blijft hij achter bij gezonde leeftijdsgenoten en wanneer de z-score toeneemt dan groeit hij sneller dan zijn leeftijdsgenoten. Voor één patiënt zijn de 9 z-scores in een figuur weergegeven. Er is te zien dat bij diagnose de z-score bijna 0,8 bedraagt en dat deze afneemt tot 2 jaar na diagnose.

Om series van dergelijke z-scores eenvoudig te kunnen analyseren, wilden we het verloop in maat en getal vastleggen. Hiertoe hebben we door de z-scores van iedere patiënt een vloeiende lijn (parabool) getrokken (zie figuur). Een dergelijke parabool is bepaald door een wiskundige formule. In deze formule is met name één getal (**b**) voor ons interessant. Dat getal geeft aan hoe groot de verandering van de groei is halverwege ons onderzoek. Deze verandering van de groei (uitgedrukt in z-scores) is, bij gezonde kinderen, gemiddeld ongeveer nul. Het verloop van de z-scores is dan een rechte horizontale lijn. Bij kinderen die achterblijven, is de verandering kleiner dan nul, en bij kinderen die inhalen groter dan nul.

Uiteraard hebben we de bruikbaarheid van bovengenoemde methode voor analyse van het verloop van de groei onderzocht. Opnieuw konden we de gegevens van de kinderen uit Nijmegen als controle gebruiken, omdat deze kinderen eveneens meerdere keren achtereen waren gemeten.

We vonden bij verschillende groepen gezonde Nijmeegse kinderen, zoals verwacht, waarden van **b** die dicht bij nul liggen. We vonden voor zithoogte echter, een waarde groter dan nul. Een sluitende verklaring hiervoor hebben we niet kunnen vinden.

We concluderen dat de beschreven methode goed te gebruiken is voor analyse van het verloop van de groei, gedurende een periode van 2 jaar. Groepen patiënten kunnen zo, ten aanzien van veranderingen in groei, onderling worden vergeleken. Ook kunnen patiëntengroepen onderling worden vergeleken of met een groep gezonde Nijmeegse kinderen.

§6. Lichaamsmaten tijdens en na behandeling.

Voor dit deel van het onderzoek konden de gegevens van 79 kinderen, ingedeeld in 8 groepen, worden gebruikt. De patiënten met een hersentumor vertoonden in het algemeen tijdens de 2 jaar van het onderzoek een toenemende achterstand in lengtegroei. Ook de groei van zithoogte en spanwijdte bleven bij deze patiënten achter. Deze achterstand is waarschijnlijk een gevolg van een hoge dosis bestraling van de schedel.

Ook de lengte van de kinderen met acute lymfatische leukemie (ALL) bleef gemiddeld tijdens de behandeling achter, echter minder dan die van patiënten met een hersentumor. Een dergelijke achterstand was eveneens aantoonbaar

voor zithoogte en spanwijdte, waarbij spanwijdte duidelijk meer achterbleef dan zithoogte. We konden weinig verschil aantonen tussen kinderen die met en zonder (een lage dosis) schedelbestraling werden behandeld. De groeiachterstand kan bij deze kinderen dus niet alleen door de bestraling worden verklaard. Ook de cytostatica en bijnierschorshormonen (zoals dexamethason en prednison) hebben waarschijnlijk een nadelige invloed op de groei gehad. Gelukkig vonden we bij een vergelijkbare groep kinderen, gevolgd vanaf het staken van de medicijntoediening, dat de achterstand voor een groot deel weer werd ingehaald.

Het gewicht in relatie tot de leeftijd bleef (gemiddeld) bij de patiënten met ALL normaal. Het gewicht in relatie tot de lengte echter, nam (gemiddeld) abnormaal toe bij ALL patiënten die dexamethason kregen als onderdeel van hun behandeling.

De lengtegroei van patiënten met een Wilms' tumor (gezwel uitgaande van de nier) bleek alleen tijdens het begin van de behandeling achter te blijven. Deze achterstand werd nog tijdens de medicijntoediening voor een groot deel weer ingehaald. De achterstand in lengtegroei hangt waarschijnlijk samen met de slechte voedingstoestand van deze kinderen in het begin van hun ziekte. Het gewicht komt vrij snel weer op peil; herstel van de lengtegroei volgt aansluitend.

De lengtegroei van de kinderen met andere, nog niet genoemde, vormen van kanker, behandeld met hoge doseringen celdodende middelen zoals cyclofosfamide en/of methotrexaat, bleek nauwelijks gestoord te zijn. Er was echter wel enige extra lengte toename aantoonbaar in een vergelijkbare groep, na het staken van de behandeling. Deze kinderen zijn mogelijk minder kwetsbaar voor groeiachterstand omdat ze over het algemeen ouder zijn dan bijvoorbeeld de patiënten met ALL of een Wilms' tumor.

De zithoogte in relatie tot de lengte hebben we onderzocht bij patiënten van wie de gehele wervelkolom of een deel ervan, bestraald was (patiënten met een hersentumor of een Wilms' tumor). Een achterstand hebben we tijdens de 2 jaar van ons onderzoek niet kunnen aantonen. Mogelijk is de periode van 2 jaar daarvoor te kort.

§7. Skeletleeftijd.

De skeletleeftijd kan onderzocht worden door middel van een röntgenfoto van de hand. De skeletleeftijd behoort bij gezonde kinderen gemiddeld overeen te komen met de echte leeftijd van een kind (kalenderleeftijd). Met andere woorden, wanneer een kind 1 jaar ouder wordt, dan neemt gemiddeld de skeletleeftijd ook 1 jaar toe.

We hebben bij 40 kinderen met ALL tijdens en/of na hun behandeling, met tussenpozen van 1 jaar, één of meer foto's van de hand gemaakt. De ontwikkeling van de skeletleeftijd bleek tijdens de behandeling, achter te blijven bij de kalenderleeftijd. Deze achterstand werd reeds tijdens de eerste 2 jaren na het staken van de medicijntoediening geheel ingehaald. Opnieuw was er geen verschil

tussen kinderen die wel en die niet op hun schedel bestraald waren. We veronderstellen daarom dat bij onze patiënten niet zozeer de schedelbestraling dan wel de behandeling met cytostatica en bijnierschors hormonen de tijdelijke achterstand in skeletleeftijd (en lengtegroei) heeft veroorzaakt.

De veranderingen in ontwikkeling van de skeletleeftijd blijken samen te gaan met de veranderingen in lengtegroei (zie §6). Achterstand in ontwikkeling van skeletleeftijd en lengtegroei ten gevolge van ziekte of behandeling komt niet alleen bij ALL patiënten voor. Een dergelijke achterstand is ook gemeld bij kinderen met ernstige, niet-kwaadaardige, aandoeningen.

§8. Puberteitsontwikkeling.

Behandeling van volwassenen met kanker kan tot gevolg hebben dat hun geslachtsorganen tijdelijk of blijvend minder goed functioneren. Wij onderzochten daarom de puberteitsontwikkeling van 43 kinderen met kanker, die bij diagnose ouder dan 8 jaar waren. Bij meisjes werd het tijdstip van eerste menstruatie, groei van schaamhaar en borstontwikkeling vastgesteld. Bij jongens werd de groei van schaamhaar en grootte-toename van de zaadballen onderzocht. Elf van de 43 kinderen bleken in meer of mindere mate een vertraagde puberteitsontwikkeling te hebben. Dit is bijna drie keer zoveel dan wat we verwachtten op grond van Engelse gegevens, verzameld in 1965.

§9. Conclusies en toekomstig onderzoek.

Ons onderzoek was bedoeld om de groei van kinderen met kanker te onderzoeken. Als men weet dat bepaalde behandelschema's groeiachterstand tot gevolg hebben, dan kan men daar rekening mee houden bij het ontwerpen van nieuwe behandelschema's.

Bij de meeste groepen patiënten bleek de groei weinig tot niet gestoord. Alleen de groep patiënten met een hersentumor vertoonde in ons onderzoek een ernstige achterstand in lengtegroei. De groepen patiënten met ALL vertoonden alleen een achterstand tijdens de medicijntoediening.

De precieze oorzaak van de groeiachterstand bij de ALL patiënten blijft voorlopig onduidelijk. De tegelijk optredende achterstand in skeletleeftijd vormt evenmin een aanknopingspunt voor een verklaring. Zowel de schedelbestraling als de medicijnbehandeling kunnen een rol spelen.

Verder onderzoek waarbij na korte tijd iets te zeggen is over de groei, is wenselijk. Met behulp van metingen van de lengte van het onderbeen kan al binnen enkele weken veranderingen van groei worden vastgesteld. Uitspraken over het effect van de kort tevoren gegeven behandeling op de groei, worden met de nieuwe methode mogelijk.

Het is natuurlijk belangrijk te weten dat bepaalde medicijnen een nadelig effect op de groei hebben. Interessanter is het, om te weten te komen hoe een dergelijk effect tot stand komt. Het is bekend dat bepaalde hormonen belangrijk zijn

voor een normale groei. Een van deze hormonen is het groeihormoon dat door het hersenaanhangsel (hypophyse) wordt gemaakt en stootsgewijs afgegeven aan het bloed. Sinds kort is het mogelijk om dit groeihormoon niet alleen in het bloed maar ook in de urine te bepalen. Omdat voor het betrouwbaar meten van de groeihormoon-afgifte altijd meerdere bloedmonsters nodig waren, kan de belasting voor de patiënt met deze methode verminderen. Urine kan meerdere keren thuis worden verzameld, zodat het effect van bepaalde behandelingen op de groeihormoon afgifte eenvoudig kan worden gemeten.